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Deferred Cord Clamping and Long-Term Neurodevelopmental Outcomes in Preterm Infants Born < 29 weeks Gestation in Southern Alberta

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by

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ABSTRACT

Importance: Deferred cord clamping (DCC) is recommended for both term and preterm infants to reduce neonatal complications; however, evidence regarding its association with long-term neurodevelopment remains limited.

Primary objective: To examine the impact of DCC compared with immediate cord clamping (ICC) on mortality and any neurodevelopmental impairment (NDI) at 18–24 and 36 months corrected age (CA) in preterm infants born before 29 weeks' gestation.

Design, setting, and participants: This retrospective cohort study included preterm infants (<29 weeks) admitted to neonatal intensive care unit between 1 January 2006, and 31 December 2011, comprised ICC group, and those born between 1 July 2012, and 31 December 2017, comprised DCC group. Neurodevelopmental assessments were conducted at 18–24 and 36 months corrected age.

Results: Of 165 infants who received DCC, 153 and 145 had outcome data available at 18–24 and 36 months, respectively. Infants in the DCC group had slightly higher gestational age at birth and a greater proportion were small for gestational age status. Compared with ICC, DCC was associated with lower odds of sepsis, severe retinopathy of prematurity, fewer blood transfusions and shorter oxygen dependence. To obtain equivalent comparison groups, a propensity score–matched analysis was conducted with adjustments for multiple confounding variables. The odds (OR) of death or any NDI at 18–24 months was 1.09 (95% CI: 0.98–1.21, p = .096), and at 36 months CA was 1.18 (95% CI: 1.06–1.32, p = .003). Cognitive assessment was performed using the WPPSI-III during the ICC period and the WPPSI-IV during the DCC period. To maintain consistency by relying on a single assessment tool (WPPSI-IV), an additional analysis was

undertaken among preterm infants who received ICC within the DCC period (July 1, 2012–December 31, 2017) and were evaluated at 36 months CA; this analysis yielded a propensity score–adjusted OR was 0.77 (95% CI: 0.64–0.90).

Conclusions: In infants born before 29 weeks' gestation, DCC was not associated with increased odds of death or NDI at 18–24 months, but by 36 months CA, it significantly reduced the risk of death or neurodevelopmental impairment.

Key words: Deferred cord clamping, Immediate cord clamping, Neurodevelopmental impairments, Preterm infants.

PREFACE

This thesis is original, unpublished, independent work by the author, D., Aditi. The experiments reported in Chapters 2-4 were covered by Ethics Certificate number REB24-0189_REN1, issued by the University of Calgary Conjoint Health Ethics Board for the project “Deferred Cord Clamping and Long-Term Neurodevelopmental Outcomes in Preterm Infants born <29 weeks gestation in Southern Alberta” on April 12, 2024.

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DEDICATION

To my parents,

Though miles apart, your unwavering support, and enduring blessings have remained a constant source of strength and motivation throughout this journey.

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LIST OF SYMBOLS AND ABBREVIATIONS

AGA: Appropriate for gestational age

ANCS: Antenatal corticosteroids

BWT: Birth weight

BPD: Bronchopulmonary dysplasia

BSID: Bayley Scales of Infant and Toddler Development

CA: Corrected age

CI: Confidence interval

CLD: Chronic lung disease

CP: Cerebral palsy

CPAP: Continuous positive airway pressure

CSF: Cerebrospinal Fluid

DCC: Deferred cord clamping

ELBW: Extremely low birth weight

EOS: Early onset of sepsis

FMC: Foothills Medical Centre

GA: Gestational age

ICC: Immediate cord clamping

IQR: Interquartile range

IVH: Intraventricular hemorrhage

LOS: Late onset of sepsis

M-H Test: Mental Haenszel test

NDI: Neurodevelopmental impairment

NEC: Necrotising enterocolitis

NICU: Neonatal Intensive Care Unit

OR: Odds ratio

PDA: Patent ductus arteriosus

PT: Placental transfusion

PTB: Preterm birth

PVL: Periventricular leukomalacia

RCT: Randomized control trial

RDS: Respiratory distress syndrome

ROP: Retinopathy of prematurity

RR: Relative risk

SGA: Small for gestational age

SD: Standard deviation

SNI: Severe neurological injury

UCM: Umbilical cord milking

WPPSI: Wechsler Preschool and Primary Scale of Intelligence

CHAPTER 1: INTRODUCTION

Preterm birth (PTB) is a major global public health concern. The World Health Organization (WHO) defines it as the birth of an infant before 37 completed weeks of gestation (GA) or less than 259 days from the first day of the mother's last menstrual period (LMP) (1). Preterm infants are highly susceptible to both immediate and long-term adverse outcomes, owing to the immaturity of the brain and other vital organs. This vulnerability is often compounded by perinatal stressors, such as antenatal infection (e.g. chorioamnionitis), hypoxic-ischaemic encephalopathy, and postnatal insults including oxidative stress, sepsis, mechanical ventilation and haemodynamic instability. Collectively, these factors contribute to severe early postnatal complications and markedly increase the risk of enduring long-term neurodevelopmental impairments. Consequently, comprehensive postnatal management is critical for improving long-term outcomes. Beyond clinical challenges, PTB imposes substantial social and economic burdens, increasing healthcare and educational costs and affecting family wellbeing (2).

Deferring umbilical-cord clamping (deferred cord clamping, DCC) at birth offers significant physiological benefits for preterm infants by enabling additional placental transfusion and supporting a smoother transition from fetal to neonatal circulation. The main objective of DCC is to promote lung aeration, establish effective pulmonary blood flow and facilitate gas exchange before clamping. These adaptations enhance oxygenation, stabilise blood pressure, raise hemoglobin concentration, support cardiorespiratory transition and reduce the risk of ischaemic injury during the shift from placental to pulmonary circulation. Extensive clinical evidence on both term and preterm infants demonstrates the safety and efficacy of DCC in reducing mortality, improving hematological parameters and mitigating short-term adverse outcomes (3).

However, findings regarding its association with long-term neurodevelopmental outcomes in preterm infants remain limited and inconsistent. Few studies have assessed whether DCC promotes achievement of age-appropriate developmental milestones. Consequently, the long-term advantages of DCC over immediate cord clamping (ICC) remain uncertain. Further robust evidence is required to clarify the role of DCC in enhancing neurodevelopment and overall neonatal outcomes, particularly among infants born at extremely preterm gestations.

Introduction to the Research Problem

Preterm birth remains the leading cause of perinatal mortality and morbidity worldwide, accounting for approximately 70% of neonatal deaths and nearly half of long-term neurodevelopmental impairments (NDIs) in infants born prematurely (4). Each year, an estimated 15 million infants are born preterm, representing approximately 11% of live births globally (5). Of these, nearly one million die annually, comprising 35% of all neonatal (aged <28 days) and 18% of all childhood deaths (aged under 5 years) (6). In Canada, preterm delivery occurs in approximately 8% of pregnancies (7), with Alberta recording the nation's highest rate in 2021, at 8.8% (8).

Beyond its contribution to mortality, PTB substantially increases the risk of early and long-term morbidities. Common short-term morbidities include respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), neonatal sepsis, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), severe neurological injury (SNI), necrotising enterocolitis (NEC) and retinopathy of prematurity (ROP). Many of these conditions result in prolonged neonatal intensive care unit (NICU) admission (9) and hinder attainment of developmental milestones, particularly those involving cognitive and motor function (10, 11). Overtime, preterm infants are at increased risk of NDIs such as cerebral palsy,

cognitive, motor, or language delays, and visual, or hearing impairments (12), often accompanied by impaired physical growth.

The risk of NDI after PTB is influenced by antenatal, perinatal, and postnatal factors. Antenatally, maternal diabetes, chorioamnionitis, malnutrition and inadequate prenatal care have been linked to suboptimal developmental outcomes. Perinatal determinants include low GA, male sex, clinical instability, need for resuscitation required at birth, hypothermia, small for gestational age (SGA) status and brain injuries such as IVH or white matter damage. Postnatally, the risk is compounded by prolonged medical complications, continued oxygen or enteral support, and socioeconomic deprivation, limiting access to early intervention and developmental support services (13).

The World Health Organization (WHO) highlights several maternal and neonatal interventions shown to improve preterm outcomes. For women at risk of preterm delivery, evidence-based measures include antenatal corticosteroids (ANCS), tocolytic therapy, magnesium sulphate, antibiotics, and careful selection of delivery mode. For infants, intervention such as, maintaining thermal stability, applying continuous positive airway pressure (CPAP), administering surfactant, and providing controlled oxygen therapy have reduced mortality and morbidity (14). More recently, placental transfusion strategies, particularly DCC, have shown significant benefits in both term and preterm infants. DCC supports a smoother physiological transition from intrauterine to extrauterine life by establishing pulmonary, cardiovascular, and cerebral hemodynamics. It also facilitates early mother-infant bonding through immediate skin-to-skin contact, promoting temperature regulation and heart rate stability. Leading professional bodies including the American College of Obstetricians and Gynaecologists (ACOG), the American Academy of Pediatrics (AAP), the Canadian Paediatric Society (CPS), and the Royal College of

Obstetricians and Gynaecologists (RCOG)—now recommend deferring cord clamping in vigorous term and preterm infants by at least 30–60 seconds or longer after birth (15).

Significance of the Research Problem

Preterm infants face substantially greater risk of mortality, major morbidities and developmental delays than those born at term, particularly when born before 32 weeks of gestation. This vulnerability reflects the immaturity of multiple organs and physiological systems. The brain undergoes rapid and critical development between 24 and 36 weeks of gestation; birth during this period markedly increases the risk of abnormal brain maturation, such as disrupted myelination and injury (IVH). These neurological insults may have lasting effects on motor, cognitive and sensory functions, leading to long-term neurodevelopmental impairments (16). The incidence of NDI correlates strongly with lower GA and reduced birth weight (17).

Advances in perinatal and neonatal care over recent decades, have substantially improved survival rates, particularly among infants born at 22–26 completed weeks' of gestation (18). A retrospective analysis of infants born at <28 weeks– and admitted to Canadian Neonatal Network sites between 2010 and 2021 reported that the average GA at NICU admission was 25.4 weeks with an overall survival rate of 85.3% (19). Similarly, a systematic review of 47 studies found survival rates of 9% (95% CI: 3–22) among infants born at 22 weeks and 55% (95% CI: 39–70) when born at 24 weeks (20). Despite these improvements, surviving infants remain at elevated risk of developmental disabilities, chronic health complications, and growth delays, often resulted in poorer academic outcomes and long-term health challenges. The associated economic burden, arising from intensive neonatal care and on-going multidisciplinary support, remains considerable. Identifying modifiable risk factors and implementing preventive and therapeutic

interventions are, therefore, essential to improving both survival and developmental outcomes in this vulnerable population.

Placental transfusion (PT) strategies, involving various approaches to umbilical cord management, can significantly influence preterm infant outcomes. Deferred cord clamping, a well-established placental transfusion method, offers considerable benefits, and is now standard practice in Canada and many other high-income countries. Evidence shows that preterm infants who receive DCC have higher haemoglobin levels and improved iron stores, reduced anemia and transfusion requirements, greater haemodynamic stability, and lower rates of BPD, IVH, NEC, and late-onset sepsis (LOS). Moreover, DCC has been linked to improved neurodevelopmental outcomes relative to immediate cord clamping (21, 22). A recent clinical practice guideline, based on findings from randomized controlled trials (RCTs), RCT meta-analyses, and observational studies confirms the effectiveness of DCC in enhancing both immediate and short-term outcomes in preterm infants. Specifically, DCC reduces mortality by about 30% in extremely preterm and overall preterm populations and significantly decreases the risk of major morbidities, such as, IVH, risk ratio (RR): 0.83, 95% CI: 0.70–0.99 and NEC, RR: 0.59, 95% CI: 0.37–0.94; as well as the need for blood transfusion, RR: 0.66, 95% CI: 0.50–0.86, and ionotropic support, RR: 0.37, 95% CI: 0.17–0.81 (3).

Although only a limited number of studies have examined the relationship between DCC and neurodevelopmental outcomes, the evidence on long-term effects remains inconclusive. A small RCT involving very preterm infants found a lower proportion of death or adverse neurodevelopmental outcomes in the DCC group than in the ICC group (21% vs 34%), with a RR of 0.61 (95% CI: 0.39–0.96) (23). Among term infants, those who received DCC demonstrated improved neurodevelopmental performance at 12 months (24); however, no

significant difference in Ages and Stages Questionnaire (ASQ) scores at 3 years compared with those who underwent immediate cord clamping (25).

Given the established benefits for immediate and short-term outcomes, and the emerging but limited evidence on long-term developmental advantages, DCC appears to be a promising intervention in PTB management. However, data from the Canadian Neonatal Network™ (CNN) indicate that, as of 2022, DCC was implemented in only 55% of extremely preterm infants (<29 weeks' gestation) admitted across 32 tertiary neonatal intensive care units (NICUs), representing 1,649 cases (26).

The paucity of literature examining long-term neurodevelopmental outcomes following DCC underscores the need for large-scale, longitudinal studies to clarify its sustained effects. Strengthening evidence on the long-term benefits of DCC could support broader implementation, particularly in centres where current uptake remains below national targets.

Literature Review

Definition and Classification of Preterm Infants

Preterm infants are defined as those born alive before completing 37 weeks of gestation. They are further classified by GA into four subgroups: extremely preterm (born at <28 weeks), very preterm (28–<32 weeks), moderately preterm (32^{+0}–33^{+6} weeks) or late preterm (34^{+0}–36^{+6}weeks). These distinctions are clinically important, as the risk of adverse outcomes rises sharply with decreasing GA, and management strategies vary accordingly (8).

Approximately 20% of PTBs are medically indicated due to maternal or fetal conditions such as pre-eclampsia, gestational diabetes, or intrauterine growth restriction. A further 20–30% result

from preterm premature rupture of membranes (PPROM), while 25–30% occur spontaneously without a clearly defined cause. Owing to the multifactorial nature of PTB, advancing understanding requires a comprehensive, interdisciplinary approach to its biological mechanisms (27).

Several maternal factors are associated with increased PTB risk. These include demographic characteristics such as Black or African American ethnicity, extremes of maternal age (<18 or > 40 years), and low socioeconomic status. Lifestyle factors– smoking, alcohol intake, inadequate prenatal care, poor nutrition, and anemia– also contribute substantially. A complex obstetric history, including previous preterm delivery, multiple gestation, and short interpregnancy intervals, further elevates risk. Medical conditions such as diabetes, thyroid disease, and hypertension, along with complications including placenta praevia, abruptio placentae, and hydramnios, are recognised contributors. Additional risk factors encompass intrauterine infection, use of assisted reproductive technologies, and mental health challenges such as stress and depression (27).

Evidence indicates that females with a history of PTB have approximately 3–7 times greater odds of recurrence than those whose first pregnancy reached full term (28, 29). A systematic review by Schaaf et al. found that females of Black ethnicity face more than double the risk of PTB (30), while a meta-analysis by Wendt et al. reported that short interpregnancy intervals—particularly those <6–12 months—are associated with significantly higher odds of preterm delivery (31). Multiple gestations account for about 15–20% of all PTBs, and both psychological stress and tobacco use during pregnancy are linked with elevated, though generally less than twofold, risk (32).

Cervical ultrasonography and fetal fibronectin testing are key diagnostic tools for assessing PTB risk. Preventive strategies include lifestyle modification, targeted antenatal interventions, and maternal therapies such as smoking-cessation programmes, low-dose aspirin, antenatal corticosteroids, progesterone supplementation, magnesium sulfate, antibiotic therapy, and appropriate pharmacological management of comorbidities (33). For preterm deliveries, timely and comprehensive neonatal care is critical, encompassing thermal regulation, infection prevention, respiratory distress management, early initiation of breastfeeding, and measures to enhance placental transfusion at birth. These interventions are central to reducing the morbidity and mortality associated with preterm birth (33).

Effective prevention and early diagnosis of PTB depend on targeted approaches addressing modifiable risk factors and prioritising high-risk populations. Improving access to and quality of preconception, antenatal, and postnatal care is vital to lowering PTB rates and optimising maternal and neonatal outcomes.

Definition of Immediate Cord Clamping (ICC)

Immediate cord clamping refers to clamping the umbilical cord almost immediately after birth, typically within <15 seconds (34). Historically, ICC became widely adopted in the 1900s, despite limited evaluation of its safety or physiological effects. This practice preceded recent research demonstrating the benefits of DCC, particularly for preterm infants (35). At birth, approximately 20–30% of the fetal-placental blood volume, including red blood cells, remains in the placenta (36). Moss and Monset-Couchard reported that residual placental blood volume following immediate clamping ranged from 85–125 ml, whereas with deferred clamping, it was markedly lower, 0–62 ml (37). ICC deprives the newborn of this essential blood volume, which can reduce cardiac output and hinder haemodynamic transition. The resultant decrease in cerebral perfusion

can lead to tissue hypoxia, increased risk of brain ischemia, multiple organ injury, or death (38). ICC is further associated with complications such as bradycardia, elevated pulmonary artery pressure causing right-to-left shunting, and fluctuations in carotid artery pressure, all of which increase NICU morbidity and mortality. Bhatt et al. demonstrated in anaesthetised fetal lambs, that ICC produced a 50% reduction in pulmonary blood flow and a sudden 40% drop-in heart rate, attributed to the sudden cessation of umbilical venous return (39).

Definition, Physiology and Types of Placental Transfusion (PT)

At birth, blood flow through the umbilical arteries and vein continues for several minutes. Placental transfusion describes the transfer of residual placental blood to the newborn during this period, providing fetal haemoglobin and improving arterial oxygen content, cardiac output, and tissue oxygenation to meet postnatal metabolic demands (40). The placenta serves as a vital organ throughout gestation, acting as a major blood reservoir for the fetus. It facilitates gas exchange, nutrient, and waste transport, hormone and growth factor production, and immune protection by maintaining a barrier between maternal and fetal systems (41).

The umbilical cord, comprising two arteries and one vein, connects the fetus to the placenta and supports this exchange. Umbilical blood flow increases to approximately 105 ml/kg/min before 20 weeks of gestation and gradually decreases to about 65 ml/kg/min at term. Between 20 and 30 weeks, placental circulation contributes approximately 30% of total fetal cardiac output. Following delivery, the umbilical arteries constrict, rapidly reducing blood flow from fetus to placenta, while umbilical venous flow persists for several minutes. Deferring the clamping of the umbilical cord during this window permits an increase in the infant’s blood volume, supporting the shift from fetal to neonatal circulation. This improved blood flow enhances the perfusion of

critical organs and is associated with a reduced risk of serious complications such as IVH and necrotizing enterocolitis (42).

The volume of placental transfusion is influenced by several factors including timing of cord clamping, uterine contractions, umbilical blood flow, onset of respiration, and gravity. Optimising these factors is essential to ensure adequate oxygenation and metabolic stability of the newborn infants (43). Placental transfusion can be achieved through four primary techniques: deferred Cord Clamping (DCC), physiological-based cord clamping (PBCC), milking of the intact cord (I-UCM) and milking of the cut cord (C-UCM) (40).

Definition of Physiological-Based Cord Clamping (PBCC) or Placental Transfusion While Intact Cord

Physiological-Based Cord Clamping (PBCC) refers to maintaining an intact umbilical cord after preterm birth until the infant's lungs are aerated and the respiratory stability is achieved. Stability is defined by the presence of regular spontaneous breathing, a heart rate ≥100 beats per minute, and oxygen saturation >90% while receiving supplemental oxygen at <40% concentration (44). In clinical practice, non-breathing infants are often clamped early and transferred to a resuscitation platform for immediate intervention. However, detaching the infant from the placental circulation before establishing respiration may adversely affect transition. An RCT involving 508 infants born at $\geq 32^{+0}$ weeks of gestation, who required resuscitation, reported comparable mean heart rates between PBCC and ICC groups (45). In a separate study using mechanically ventilated preterm lambs resuscitated with 100% oxygen, PBCC prevented initial hypoxia and reduced subsequent hyperoxia. Nonetheless, PBCC did not reduce lung oxidative stress, inflammation, or structural injury, nor did it reduce the severity of ventilation related lung

damage (46). Research on PBCC in preterm infants remains limited, and current evidence does not consistently demonstrate significant clinical benefits.

Definition and Types of Umbilical Cord Milking (UCM)

Umbilical cord milking (UCM) involves gently squeezing 20–30 cm of the umbilical cord from the placenta toward the newborn, usually three to five times at a rate of approximately 10 cm per second. The procedure can be performed while the cord remains intact or after it has been clamped and cut. It is particularly beneficial in critically compromised infants, because it can be completed within 10–20 seconds, nearly as quickly as ICC– allowing for prompt initiation of neonatal resuscitation (47). The principal aim of UCM is to deliver the maximal placental blood volume to the newborn, achieving near-complete placental transfusion in less time than deferred cord clamping. An RCT of preterm infants (<32 weeks' gestation) showed that those who received UCM had significantly higher heart rates and oxygen saturation during the first five minutes of resuscitation, required less inspired oxygen in the first 10 minutes, and a greater proportion did not require supplemental oxygen in the delivery room. In the subgroup, of infants <26 weeks, all 10 in the ICC group required oxygen, whereas only 3 of 5 in the UCM group did (48). Conversely, an RCT of infants born 28–32-weeks, found no significant difference in severe IVH or mortality, between the UCM and DCC groups; rate difference 0.01%, 95% CI: (−1.4% to 1.4%), p=0.99) (49). Given these conflicting findings, current evidence regarding UCM in preterm infants, particularly those born at <29 weeks' gestation, is insufficient to recommend routine implementation. Further well-designed trials are needed to evaluate its potential benefits and risks, including the incidence of IVH, before widespread adoption in this high-risk population (50, 51).

Definition, Physiology and Types of Deferred Cord Clamping (DCC)

Deferred cord clamping (DCC) involves postponing the clamping of the umbilical cord after birth to permit continued placental transfusion to the newborn. The delay typically ranges from ≥15 seconds (21) to 3–5 minutes after birth (52), or until umbilical cord pulsation ceases (53). DCC provides substantial benefits for both term and preterm infants by reducing the incidence of several perinatal complications (54).

Fetal circulation is a transient and physiologically distinct system, that differs markedly from neonatal and adult circulation. In preterm infants, transition to extrauterine life occurs before circulatory maturation is complete, having an understanding of fetal physiology is essential for managing haemodynamic compromise (55). Before birth, the umbilical cord serves as the vital conduit between the placenta and the fetus, facilitating the exchange of oxygen and nutrients. Owing to high pulmonary vascular resistance, fetal pulmonary blood flow remains limited, and gas exchange occurs primarily through the placenta, a low-resistance vascular circuit. Oxygenated blood from the placenta enters the fetal system via the umbilical vein and is shunted through the ductus venosus to the inferior vena cava. It then by-passes the lungs through a patent foramen ovale, directing a large portion of blood from the right to the left atrium, while the ductus arteriosus channels flow from the pulmonary artery into the aortic arch (56).

Lung aeration is the critical event initiating the cascade of physiological adjustments required for successful transition to neonatal life. The onset of spontaneous respiration introduces atmospheric oxygen to the pulmonary circulation, triggering rapid vasodilation and increased right ventricular output, and enhanced venous return. This process enables substantial transfusion of blood from the low-resistance placental circuit to the infant. Premature clamping of the cord,

before effective respiration, leaves a significant proportion of blood volume within the placenta, reducing left ventricular preload, and compromising cardiac output (57).

In preterm birth, immediate cord clamping, especially before the onset of spontaneous ventilation, can lead to a sustained 50% reduction in venous return, ventricular preload, and cardiac output, thereby increasing the risk of hypoxic-ischemic injury. This initial hypoperfusion is often followed by a sharp rise in output as pulmonary flow increases, producing considerable fluctuations in systemic blood pressure and flow. Such hemodynamic instability is strongly implicated in the development of IVH in preterm infants. By contrast, DCC allows sufficient time for pulmonary aeration to occur before the cord occlusion. The resulting rise in pulmonary blood flow compensates for the loss of umbilical venous return, maintaining cardiac output and ensuring a smoother cardiovascular transition. This mechanism stabilises systemic circulation, facilitates placental transfusion, and mitigates abrupt pressure fluctuations associated with IVH (58).

According to Yao et al., DCC enables progressive blood transfer from the placenta to the infant, producing a steady rise in infant blood volume and a parallel decline in placental blood volume. The distribution of blood between the infant and placenta varies with clamping time: approximately 67% / 33% at birth, 80% / 20% at 1 minute, and 87% / 13% at the completion of placental transfusion (59).

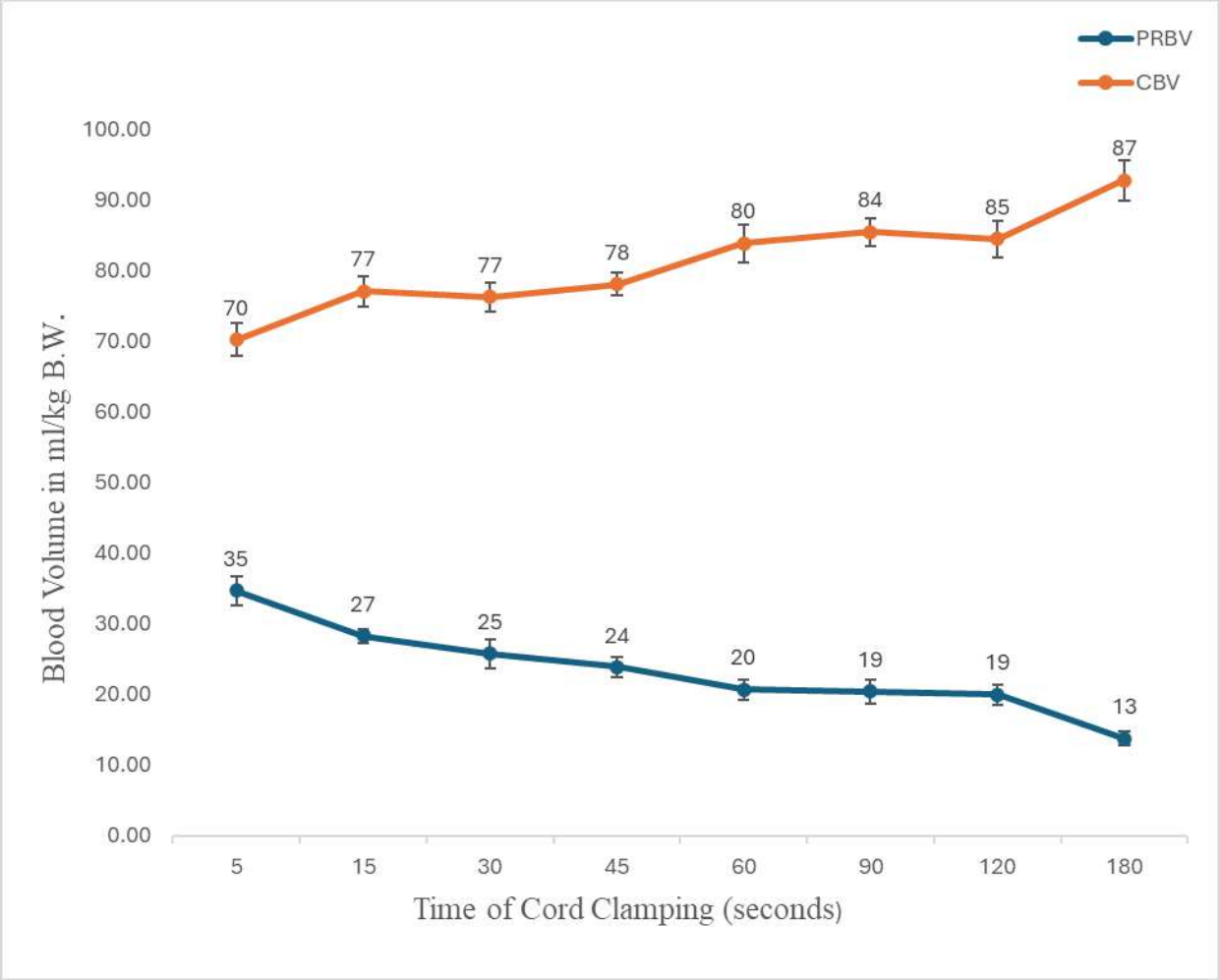

Figure 1. Relationship between complete blood volume in Infants (CBV) and Placental residual blood volume (PRBV) at different umbilical cord clamping times (Yao et al.)

DCC can be practised at three distinct time intervals, for example, short deferral (≥15 to < 45 seconds), medium deferral (≥45 to <120 seconds) and long deferral (≥ 120 seconds) (60).

Effect of DCC on preterm infants

After birth, newborns undergo rapid physiological adaptations, particularly within the respiratory, cardiovascular, central nervous, and endocrine systems (61). The respiratory and cardiovascular systems change almost immediately, whereas other organs adapt more gradually

as the transition from intrauterine to extrauterine life progresses. In preterm infants, these adaptive processes are often impaired due to organ immaturity (62), predisposing them to adverse neonatal outcomes and long-term neurodevelopmental impairments (63).

High-certainty evidence indicates that umbilical cord clamping strategies, particularly DCC, can improve clinical outcomes in PTBs (64) without increasing maternal or neonatal risk (65). Most studies report that preterm infants receive DCC for at least 30 seconds, exhibit higher haemoglobin and haematocrit levels, reduced anaemia, improved hemodynamics, higher systemic blood pressure and urine output, enhanced cardiac function, and decreased need for vasopressors and transfusions. DCC has also been linked to lower rates of BPD, IVH (all grades), NEC, LOS compared with immediate cord clamping (21, 54, 66). As most preterm infants begin breathing within the first 60 seconds, maintaining cord integrity during this interval can reduce the need for invasive procedures such as endotracheal intubation and mechanical ventilation. These interventions are associated with higher risks of death or NDIs, due to inflammatory responses, ionotrope exposure, delayed feeding initiation, and development of bronchopulmonary dysplasia (67). DCC has been shown to lower overall mortality by approximately 30% in both extremely preterm and other preterm infants. Two recent meta-analyses of RCTs reported a RR of 0.70, 95% CI: 0.51–0.95 for extremely preterm infants, and 0.73, 95% CI: 0.54–0.98 for preterm infants (3). Moreover, the transfer of immunoglobulins and stem cells through DCC may promote tissue repair following cellular injury, and inflammation, supporting long-term organ function and development.

DCC and Neonatal Morbidities

DCC and Respiratory Distress Syndrome (RDS)

Respiratory distress syndrome (RDS) remains a major complication among preterm infants, particularly those born before 30 weeks of gestation, primarily due to inadequate or delayed surfactant production in structurally immature lungs. Approximately 93% of infants born between 22–28 weeks are affected (68), with greater severity observed in those of lower gestational age and birth weight. Despite advances in antenatal corticosteroids therapy, exogenous surfactant use, and neonatal respiratory support—RDS continues to be a leading cause of morbidity and mortality in the preterm populations (69). It is also a principal reason for NICU admissions and contributes significantly to long-term NDIs, particularly in low- and middle-income countries (70, 71). The vulnerability of preterm lungs is heightened by surfactant deficiency, underdeveloped airways, and oxidative stress caused by limited antioxidant defences (72). Infants born before 32 weeks, frequently require mechanical ventilation soon after birth, and oxygen supplementation during initial stabilization can further increase oxidative stress. Male infants are more severely affected due to the inhibitory effect of androgens on lung maturation and surfactant synthesis (72). In one retrospective cohort study involving 288 mechanically ventilated preterm infants, born at <28 weeks GA, 17% developed cerebral palsy and 49% had a mental developmental index < 70 at 18 months' corrected age (73). The DCC approach, which allows ventilation prior to cord clamping, has been shown to improve cardiac output by increasing pulmonary blood flow, raise mean blood pressure and haemoglobin levels, and oxygen delivery to vital organs. Consequently, this strategy reduces the need for interventions such as endotracheal intubation and mechanical ventilation, thereby lowering the incidence and severity of RDS and improving long term outcomes (67, 74, 75).

DCC and Bronchopulmonary Dysplasia (BPD)

Extremely preterm infants are born before alveolar development begins, resulting in failed septation and a reduced number of alveoli. Bronchopulmonary dysplasia (BPD) was first described in 1967 by Northway, as a chronic lung disease in premature infants who required prolonged mechanical ventilation and oxygen therapy (76). Today it is recognised as the most common chronic lung disease of infancy, primarily affecting those born at 23–28 weeks of gestation. The condition results from a multifactorial process involving lung immaturity, surfactant deficiency, and exposure to volutrauma, atelectrauma, ventilator-associated injury, and oxidative stress (77). Preventing BPD remains a major goal in neonatal care, as it is associated with considerable morbidity and mortality. Affected infants frequently experience long-term complications, including adverse neurodevelopmental outcomes, reduced respiratory function in childhood and adulthood, impaired growth, prolonged hospitalisation, and increased healthcare utilisation compared with infants without bronchopulmonary dysplasia (78). Despite advances in neonatal intensive care, BPD continues to affect more than 50% of survivors born before 28 weeks' gestation (79). These infants often exhibit multisystem sequelae, including smaller head circumference, cerebral palsy (CP), and cognitive and language deficits. Predictors of poor neurodevelopmental outcomes include prolonged use of positive-pressure ventilation, severe IVH (grade III–IV), and discharge at >43 weeks' post menstrual age (76). Emerging evidence indicates that DCC may mitigate several complications of preterm birth. DCC increases blood volume, improves early postnatal organ perfusion, reduces the need for transfusions and decreases the incidence of IVH, BPD, NEC, and other morbidities. It also improves iron stores and enhances long-term neurodevelopment, and reduces mortality (42). In a retrospective review of 538 very low birth weight infants born between 2016–2020, Patel et al. reported that red blood

cell (RBC) transfusion was associated with an eight-fold increase in BPD risk. Infants who underwent DCC were 55% less likely to require transfusion than those who underwent other placental transfusion techniques (80).

DCC and Patent Ductus Arteriosus (PDA)

Patent ductus arteriosus (PDA) refers to the persistence of the fetal vascular channel between the pulmonary artery and aorta, which normally closes spontaneously within the first three days after birth. In preterm infants, particularly those born at 25–28 weeks' gestation, closure is delayed in up to 80% of cases (81). The duration of ductal patency is inversely related to GA, with earlier births associated with prolonged persistence (82). This delay results from immature ductal smooth muscle and underdeveloped oxygen-sensing mechanisms. Persistent PDA presents a significant clinical challenge, in preterm infants. The extent of left-to-right shunting and the phenomenon of ductal steal determine clinical severity. In extremely preterm infants, reduced pulmonary vascular resistance increases shunting through the ductus, leading to excessive pulmonary blood flow, interstitial edema and left ventricular volume overload. These haemodynamic changes contribute to prolonged ventilatory dependence, and increase the risks of BPD, NEC or focal intestinal perforation, IVH, and mortality. The incidence of PDA persisting beyond three days exceeds 50% among infants born at ≤ 28 weeks' gestation, with 60%–70% requiring pharmacological or surgical closure (83). Placental transfusion strategies, such as DCC, enhance systemic perfusion during the immediate postnatal period and have been associated with lower incidences of IVH, NEC and neurodevelopmental impairments (42).

DCC and Neonatal Sepsis

Preterm infants are particularly vulnerable to sepsis during both the perinatal and

postnatal periods due to immature organ systems, fragile integument, and exposure to novel antigens, such as hospital-acquired microbes, medical devices, pharmaceuticals, and nutritional sources (84). Neonatal sepsis is classified by the timing of onset into early-onset sepsis (EOS) or late-onset sepsis (LOS). Early onset sepsis typically occurs within 72 hours of life and is primarily the result of vertical maternal transmission, whereas LOS develops after 72 hours and is usually acquired horizontally from the environment, though maternal transmission may also contribute (85). The incidence of EOS is inversely proportional to GA, with approximately 20 cases per 1,000 live births in infants born <29 weeks' gestation and up to 32 cases per 1,000 in those born at 22–24 weeks. Preterm births associated with maternal complications such as cervical incompetence, preterm labour, premature rupture of membranes, chorioamnionitis, or unexplained fetal distress, carry the highest risk and often warrant empirical antibiotic therapy (86). Sepsis in preterm infants significantly increases the risk of severe IVH, PVL and NEC, which may lead to multi-organ dysfunction or neurological injury. The combined effect of infection, inflammation, comorbidities (including severe IVH, PVL and NEC), prolonged hospitalisation with extensive medical interventions contribute substantially to the risk of neurodevelopmental impairments (87-89). Using data from the NICHD Neonatal Research Network, a cohort study by Stoll et al. found that extremely low birth weight (ELBW) infants with neonatal infections had significantly greater odds of adverse neurodevelopmental outcomes, including higher rates of cerebral palsy, lower Mental and Psychomotor Developmental Index (MDI and PDI) scores, visual impairment, and suboptimal head growth, compared with uninfected infants (90). Deferred cord clamping has been shown to enhance blood volume and confer protective effects, including reduced risks of IVH, NEC, LOS and shorter hospitalisation – factors closely linked to improved long-term outcomes(47). A randomised controlled trial

comparing 45– second versus 60– second DCC in singleton infants born between $23^{0/7}$–$31^{6/7}$ weeks' gestation reported a significantly lower rate of culture-confirmed sepsis in the 60 second group (8%) compared with the 45 second group (18%; p = 0.04) (91). Conversely, a retrospective study by Lodha et al. found that DCC was associated with slightly higher, though statistically non-significant odds of LOS (AOR 1.02, 95% CI: 0.85–1.22), among infants born at 22–28 weeks' gestation (92).

DCC and Intraventricular Haemorrhage (IVH)

Intraventricular haemorrhage (IVH) is a common intracranial complication of preterm birth and a major contributor to mortality and adverse neurodevelopmental outcomes (93). Prognosis correlates strongly with haemorrhage severity. Severe IVH predominantly affects infants born before 29 weeks' gestation (94) and markedly increases the likelihood of long-term neurodevelopmental outcomes, including seizures, cognitive and executive dysfunction, and cerebral palsy (95). A retrospective cohort study by Lodha et al. reported that at three years' corrected age, 58% of infants born prior to 29 weeks' gestation with severe IVH exhibited at least one major impairment— 12% were blind, 2.6% had hearing loss, and 42% were diagnosed with moderate to severe cerebral palsy (p = 0.004) (96). Gestational age remains the strongest non-modifiable predictor of IVH, with lower GA linked to higher risk. Contributing factors include an immature coagulation profile, fragile germinal matrix vasculature, impaired cerebral autoregulation, and the frequency of complications and interventions associated with extreme prematurity (97). Among infants born before 28 weeks' gestation, the reported incidence of severe IVH is approximately 15%, while IVH of any grade affects approximately 34% (98). Strategies aimed at preventing IVH are, therefore, critical for improving neurological outcomes. In a pilot study of infants born before 28 weeks, Vesoulis et al. found that DCC significantly

reduced the incidence of IVH of any grade compared with ICC, 20% vs 50%; p = 0.04 (99). Similarly, an RCT, by Katheria et al. involving 474 infants born before 32 weeks' gestation, compared UCM and DCC, found that UCM was associated with a significantly higher incidence of severe intraventricular haemorrhage (8% [20/236] vs 3% [8/238]); risk difference, (5% [95% CI: 1%– 9%]) (100).

DCC and Periventricular Leukomalacia (PVL)

Periventricular leukomalacia (PVL) represents a major neuropathological form of brain injury in premature infants, frequently resulting in long-term neurological complications such as motor impairment, cognitive deficits, cerebral palsy and intellectual disability. The principal contributing factors include immature vascularisation of the cerebral white matter, ischaemic injury secondary to impaired cerebral blood flow regulation, and the heightened vulnerability of oligodendrocyte precursor cells to oxidative stress caused by ischemia–reperfusion events (101). PVL occurs in approximately 1.9% of infants born before 32 weeks' gestation (102). A retrospective review of children with moderate to severe PVL revealed high rates of neurological and developmental disorders, 69.7% developed cerebral palsy, 29% experienced epilepsy, and 15.6% exhibited microcephaly (103). Involvement of the optic radiation further contributes to visual dysfunction in preterm infants (104). At present, no targeted therapies exist for PVL prevention. Management strategies focus on preserving cerebral perfusion immediately after birth; hence, DCC at preterm delivery, has been increasingly implemented to enhance circulatory stability, mitigate brain injury, and potentially reduce PVL incidence (105).

DCC and Severe Neurological Injury (SNI)

Severe neurological injury (SNI) is defined as grade 3 or 4 IVH and / or periventricular

leukomalacia (PVL) (106). Key risk factors include low GA and birth weight, out born delivery (birth outside tertiary centres), use of vasopressors, mechanical ventilation, and episodes of acute clinical deterioration. Although improvements in neonatal care have increased survival rates among preterm infants, these gains have also been accompanied by a higher prevalence of neurocognitive and motor impairments, as well as long-term neurodevelopmental disabilities. Approximately 50%–75% of preterm infants surviving severe IVH develop lasting neurological sequelae (107). Deferred cord clamping has been shown to improve cardiovascular transition at birth by preventing low cardiac output states, enhancing right ventricular and superior vena cava flow, stabilizing blood pressure, and reducing the need for intensive resuscitation. Collectively, these benefits contribute to fewer adverse neurological outcomes. A large retrospective cohort study of infants born at 22–28 weeks' gestation, by Lodha et al. demonstrated that DCC was associated with a 20% reduction in the likelihood of severe neurological injury (adjusted odds ratio 0.80, 95% CI: 0.64–0.99) (92).

DCC and Necrotising Enterocolitis (NEC)

Necrotising enterocolitis (NEC) remains one of the most severe gastrointestinal emergencies in preterm infants. It is characterised by intestinal mucosal necrosis, and clinical features including feeding intolerance, bloody stools, cardiorespiratory compromise, and haemodynamic instability (108). Major risk factors include prematurity, low birth weight, formula feeding, and neonatal infection (109). Among very low birth weight infants (birth weight <1500 gram), NEC incidence ranges from 6%–15%, with mortality between 30% and 50% (110). Despite advances in NICU practices, morbidity and long-term outcomes among survivors remain poor. Complications such as NDI and intestinal failure, occur in approximately 24.8% and 15.2% of affected infants, respectively (111). Evidence indicates that placental transfusion techniques- particularly DCC

and UCM, are associated with a reduced incidence of NEC in preterm populations. A 2012 Cochrane review including 15 studies (738 infants born at 24–36 weeks' gestation, reported a significantly lower NEC risk when DCC was performed for 30–120 seconds (5 trials; 241 infants; RR: 0.62 [CI: 0.43–0.90]) (112). Similarly, a systematic review of six RCTs found a statistically significant reduction in NEC incidence in the DCC group (RR: 0.59, 95% CI: 0.37–0.94) (113).

DCC and Retinopathy of Prematurity (ROP)

Retinopathy of prematurity (ROP) is a proliferative disorder of the retinal vasculature and a major cause of preventable childhood blindness and visual impairment worldwide. The increasing incidence of preterm births, coupled with improved neonatal survival but inconsistent standards of neonatal care and delayed diagnosis, has contributed to rising rates of ROP related blindness. The risk of ROP is inversely correlated with GA and birth weight. Approximately 65% of infants with a birth weight <1,250 gram and around 80% of those weighing 1,000 gram develop some form of retinopathy of prematurity (114). A multicentre retrospective cohort study by Dai et al., involving infants born at 23– 27^{+6} weeks' gestation and admitted to NICUs within 72 hours of birth, reported that 62% developed ROP of varying severity (115). Beyond prematurity and low birth weight, postnatal factors contributing to ROP include prolonged oxygen exposure, IVH, apnoea, mechanical ventilation >7 days, neonatal sepsis, anaemia, transfusion of blood products, and poor postnatal weight gain (<50% of the birth weight) within six weeks of life (116, 117). The retina shares embryological and vascular origins with the brain through the optic nerve, rendering both organs susceptible to similar pathological processes. Consequently, extremely preterm infants who develop severe ROP are at increased risk for NDIs, including cerebral palsy, developmental delays and cognitive deficits, reflected by lower scores

in verbal IQ, performance IQ, and spatial reasoning (118). Deferred cord clamping promotes placental transfusion, augments neonatal blood volume, and reduces the need for red blood cell transfusion. It is also associated with decreased incidences of IVH, NEC, sepsis, as well as improved cardiovascular stability and cerebral oxygenation, factors closely linked to ROP development in preterm infants (80, 119).

DCC and Neurodevelopmental Outcomes

Research examining the association between DCC, neonatal complications of preterm birth, and long-term neurodevelopmental outcomes has largely focused on cord clamping practices at delivery. As a placental transfusion strategy, DCC has been shown to reduce immediate complications in preterm infants and positively influence neurodevelopmental trajectories. Evidence across multiple studies suggests that DCC increases blood volume and haemoglobin concentration which contribute to improved outcomes, for conditions such as IVH, NEC, BPD, ROP, and other sequelae of preterm birth (120, 121).

Several investigations have reported favourable long-term neurodevelopmental outcomes in preterm infants following DCC. A retrospective analysis of infants born between $22^{0/7}$ and $26^{6/7}$ weeks'' gestation within the neonatal research network (NRN) found that those receiving DCC had significantly lower odds of death or severe NDI than those who underwent immediate cord clamping (adjusted odds ratio, OR: 0.64, 95% CI: 0.50–0.83) (122). A single blind RCT involving term singleton infants, found that the DCC group exhibited increased myelin content and greater white matter volume in brain regions associated with motor, sensory and visuospatial functions. However, developmental assessment using the Mullen Scales of Early Learning, revealed no significant group differences in verbal or non-verbal domains (123). Another RCT assessing infants born at 24–31^{+6} weeks' gestation found no significant difference in Bayley

Scales of Infant Development (BSID) scores at 7 months' follow-up. Nonetheless, after adjustment for confounding factors, such as GA, IVH, BPD, sepsis and male sex; the DCC group demonstrated motor scores more than one standard deviation higher than those in the ICC group (124). In one trial, the proportion of infants with death or adverse neurodevelopmental outcomes was significantly lower in the DCC group (21%) than in the ICC group (34%), corresponding to a RR of 0.61 (95% CI: 0.39–0.96); and a risk difference of −13% (95% CI: −25%– −1%) (23).

Follow-up studies suggest that early neurodevelopmental assessments, particularly before 12–18 months, may have limited predictive value for later cognitive and motor outcomes (125-128). Evaluations conducted at 18–24 months' CA may not reliably forecast performance at 3–5 years. Although international bodies such as the World Health Organization (WHO), advocate for DCC, limited research has specifically examined its impact on neurodevelopment beyond infancy in preterm populations, especially at 3–5 years corrected age. Existing studies often involve small sample sizes and produce inconsistent findings, limiting generalisability (125, 129, 130).

Despite well-documented short-term neonatal benefits, DCC is not yet universally practised in preterm care. Barriers to its widespread implementation include uncertainty about long-term advantages and concerns regarding potential complications, such as hyperbilirubinemia, polycythemia, hypothermia, and delayed resuscitation in infants with poor respiratory effort. Moreover, substantial knowledge gaps persist due to methodological limitations, including small cohorts, single centre designs, heterogenous assessment tools, absence of standardized protocols, limited multidisciplinary follow-up, and variation in timing of evaluations (131).

Given these gaps, this study hypothesised that DCC improves survival among infants

born before 29 weeks' gestation and is associated with superior neurodevelopmental outcomes at both 18–24 and 36 months' corrected age. Accordingly, the objective of this research is to investigate the relationship between DCC and death or long-term neurodevelopmental impairments in infants born before 29 weeks' gestation in Southern Alberta.

Research Questions

Primary Research Question

What is the impact of DCC on mortality or long-term neurodevelopmental impairments (NDI) at 18–24 months and 36 months' CA in preterm infants born before 29 weeks' GA in Southern Alberta?

Secondary Research Questions

- Are there differences in mortality or rates of severe NDI between infants (born at <29 weeks' gestation) who received deferred cord clamping and those who underwent immediate cord clamping?
- Do individual long-term neurodevelopmental outcomes—specifically cerebral palsy (CP), cognitive delay, hearing impairment, and visual impairment—differ between the DCC and ICC group infants (born at <29 weeks' GA)?
- Does DCC influences short-term neonatal outcomes, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), surgical ligation of PDA , neonatal sepsis, intraventricular hemorrhage (IVH), severe IVH, severe neurological injury (SNI), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), severe ROP, and the need for oxygen at discharge?

- Are there differences in postnatal growth outcomes at 18–24 months and 36 months' CA among infants (born at <29 weeks' GA) in the DCC and ICC groups?

Objectives

Primary Objective

To evaluate the impact of DCC on mortality or long-term neurodevelopmental impairments at 18–24 months and 36 months' CA in preterm infants born before 29 weeks' GA in Southern Alberta.

Secondary Objectives

In preterm infants born before 29 weeks' GA:

- To determine differences in mortality or severe NDI between infants who received DCC and those who underwent immediate cord clamping (ICC).
- To compare the individual long-term neurodevelopmental outcomes—specifically cerebral palsy, cognitive delay, hearing impairment, and visual impairment—between the DCC and ICC groups.
- To assess the influence of DCC on short-term neonatal outcomes, including RDS, BPD, PDA, surgical ligation of PDA, neonatal sepsis, IVH, severe IVH, PVL, SNI, NEC, ROP, severe ROP and the need for oxygen support at discharge.
- To evaluate postnatal growth outcomes at 18–24 months and 36 months' CA between DCC and ICC groups?

Significance of the Study

Deferred cord clamping has been increasingly studied in preterm populations across diverse clinical settings (3, 21, 34, 54, 66, 67, 132). However, a significant gap persists regarding its long-term effects on neurodevelopmental outcomes in infants, those born before 29 weeks' gestational age. Existing studies are limited by small sample sizes, short follow-up durations, and methodological heterogeneity.

This study seeks to address these gaps and contribute robust evidence in several key areas:

- While prematurity itself remains a major independent predictor for adverse neurodevelopmental outcomes, substantial variability exists in the severity and type of impairment among affected infants. This heterogeneity suggests that modifiable perinatal factors, such as cord management strategies, may influence neurological prognosis. Identifying and evaluating such modifiable factors—particularly DCC—could provide opportunities to reduce brain injury and optimise neurodevelopmental recovery in this vulnerable population.
- Few studies have comprehensively examined both immediate outcomes and long-term developmental outcomes in infants born before 29 weeks' GA, who received deferred cord clamping. Follow-up data at later stages, particularly at 36 months' CA, are scarce due to challenges, including cohort attrition, limited sample sizes, and inconsistencies in neurodevelopmental assessment methods. Consequently, current evidence remains insufficient to establish the long-term safety and efficacy of DCC in this population.
- This study draws on a relatively homogeneous cohort of preterm infants delivered at a tertiary perinatal centre, Foothills Medical Centre (FMC), where a protocol-driven DCC approach has been employed. By analysing outcomes in this well-defined population, the research provides a clearer understanding of the potential benefits or risks associated with

DCC. The study also adjusts for key maternal and neonatal factors known to influence neurodevelopment, thereby strengthening the internal validity and clinical applicability of its findings.

- Importantly, this research incorporates a large sample size, extended longitudinal follow-up, and standardised neurodevelopmental assessments conducted at 18–24 and 36 months' corrected age. This design strengthens the reliability of the findings and increases the clinical relevance of the outcome measures.

The findings will inform evidence-based neonatal care, guide clinical-decision making and assist clinicians in counselling families regarding prognosis and long-term developmental expectations. By generating high-quality data on the relationship between DCC and neurodevelopmental outcomes in preterm infants, this study has the potential to influence neonatal policies and improve standards of care within NICUs in Canada and internationally.

CHAPTER TWO: METHODOLGY

This chapter outlines the research methodology used in the study. It describes the study design, sampling strategies, data collection processes and analytical techniques applied to draw conclusions.

Study Design

This population based retrospective cohort study involved creating exposed and unexposed groups based on two different cord clamping procedures. Both exposure and outcomes of interest occurred before study initiation. The study population comprised preterm infants, delivered at the Foothills Medical Centre (FMC) at <29 weeks' gestational age (GA) and admitted to neonatal intensive care unit (NICU) for ongoing care. Infants born between 1 January 2006, and 31 December 2011 (period 1), who received immediate cord clamping (ICC), formed the ICC group (unexposed). Those born between 1 July 2012, and 31 December 2017 (period 2), who received deferred cord clamping (DCC), formed the DCC group (exposed). A 6- month washout period (1 January–30 June 2012) separated the two cohorts. During the washout period, all staff members- including neonatologists, NICU nursing staff, Neonatal-Perinatal Medicine residents, respiratory therapists, nurse practitioners, obstetricians, low-risk maternity physicians, and nursing staff in delivery room (DR) and operating room (OR), as well as residents in DR and in NICU–were trained and educated in the DCC procedure. Neurodevelopmental outcomes of eligible preterm infants were assessed up to 36 months corrected age (CA) at the regional neonatal follow-up clinic (NFC).

Infants were categorised according to the cord clamping method they received at birth. The exposed group included infants born during period 2 who underwent DCC, whereas the

comparison group included those born during period 1 who underwent ICC. To minimise the "healthy worker effect" and reduce selection bias, infants born in the DCC period (period 2) who underwent ICC due to an immediate need for resuscitation of the newborns or mothers were excluded from the study, as they were relatively unwell (133). Both groups were followed at the NFC first at 18-24 months and then at 36 months CA to assess long-term neurodevelopmental outcomes, mortality and growth.

Because existing data on preterm infants managed with DCC or ICC were available and could be linked to neurodevelopmental follow-up records, a retrospective cohort design was deemed appropriate for this study.

Study Population

We identified all preterm infants (born <29 weeks GA) who were admitted to the NICU at Foothills Medical Centre. Following the application of the inclusion and exclusion criteria outlined below, the study sample was followed up at 18–24 months and again at 36 months CA to assess neurodevelopmental outcomes.

Inclusion Criteria

Infants were included in the study if they met the criteria below:

- Born at <29 weeks gestational age
- Admitted in the NICU at FMC, Alberta, Canada
- Had information available on cord clamping, whether DCC or ICC was received at birth
- Born between 1 January 2006, and 31 December 2011 **(period 1)** and between 1 July 2012, and 31 December 2017 **(period 2)**
- Outcome data available at 18–24 months and 36 months corrected age

Exclusion Criteria

Infants meeting any of the following criteria were excluded:

- Chromosomal abnormalities
- Major congenital anomalies
- Born to mothers with antepartum haemorrhage
- Born during the washout period
- Missing cord-clamping information in the database
- Born during the DCC period but received ICC due to maternal or neonatal complications
- Outcome data were not available at 18–24 months and 36 months corrected age

These conditions were excluded from the analysis as each carries an independent risk for adverse neurodevelopmental outcomes and could have introduced confounding and potential bias, limiting the validity of the comparisons between exposure groups.

Location of the Study

The FMC in Calgary serves as a tertiary perinatal referral centre and houses a Level 3 NICU, providing comprehensive care for high-risk preterm infants across Southern Alberta. Alberta reported one of the highest preterm birth rates in Canada (8.8%) (134). Annually, approximately 17,250 infants are born in Calgary, of whom an estimated 1,550 are born preterm. Among these, more than1,200 require specialised NICU care (135). Southern Alberta bears a higher burden of critically ill preterm births, with nearly one in 8 infants requiring NICU admission. The NICU at FMC admits approximately 1,200 infants yearly (136).

Sample Size

The sample size for this retrospective cohort study was determined using power analysis to ensure that the study retained sufficient statistical power to detect a clinically meaningful difference between the exposed and unexposed groups.

The study followed a retrospective cohort design to evaluate long-term neurodevelopmental outcomes in preterm infants, with the primary outcome being neurodevelopmental impairment (NDI). The objective was to assess the impact of DCC compared with ICC on neurodevelopmental outcomes at 18–24 months and 36 months CA in infants born at <29 weeks gestational age. A randomized controlled trial (RCT), by Armstrong-Buisseret reported an NDI rate of 34% among infants who underwent ICC (23).

The power analysis incorporated several factors: estimated effect size (RR), expected difference in NDI (based on previous studies), a two-sided significance level (α) = 0.05, and the proportion of ICC infants who developed NDI (0.34) in prior research (23).

Using these parameters, the power was calculated using the formula for comparing proportions in two independent groups, as presented by Kelsey et al. (Table 2, p. 330) (137).

$\mathbf{Z_\beta = [n(d^*)^2 r/(r+1)\ \bar{p}(1-\bar{p})]^{1/2} - Z_{\alpha/2}}$, Where:

- n = 153(18-24 months follow-up), 145 (36 months follow-up)
- Difference, $d^* = P1-P0 = -0.14$
- Unexposed to exposed ratio, r = 2
- Weighted average of P1 and P0, $\bar{P} = P1 + rP0/1+r = 0.29$
- $Z_{\alpha/2}$ is the critical value for a two-tailed test at α=0.05 (1.96)

The analysis showed that the study's power to identify a RR of 0.60 was 87.5% for 18–24 months analysis, and 85.8% for 36 months analysis. This indicates that the study sample was

sufficiently large to provide statistical reliability and validity to detect a meaningful effect size at the desired relative risk level.

Data Collection Procedure

Following approval from the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary, data were obtained from the administrative neonatal database at Foothills Medical Centre. The dataset included all preterm infants born at GA <29 weeks and admitted to the Level 3 NICU at FMC between 1 January 2006 and 31 December 2017. Each case was reviewed to confirm eligibility according to the predefined inclusion and exclusion criteria. The dataset included identifying variables such as the FMC patient identification number, date of birth, name, and residential postal code, which were used solely for internal linkage and verification in accordance with approved ethical guidelines.

Standardised demographic, perinatal and neonatal data were collected by a trained research coordinator from the patients' charts and entered into the database upon discharge from the neonatal intensive care unit. These included maternal age, educational status, residential postal code, pregnancy induced hypertension (PIH), gestational diabetes, chorioamnionitis, mode of delivery, antenatal corticosteroid use (ANCS), antibiotic use during labour, parity, multiple birth, prolonged rupture of the membrane (PROM), smoking or alcohol exposure during pregnancy, and the type of cord clamping performed at delivery. Neonatal characteristics include GA, birth weight, sex, and Apgar score at 5 minutes etc. Short-term outcome data were also collected, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), neonatal sepsis, intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP), discharge home on oxygen, number of packed red cell / whole blood transfusions, duration of

mechanical ventilation, duration of non-invasive respiratory support, duration of oxygen support, length of NICU stay (days) and mortality. Maternal socioeconomic status was assessed by linking residential postal codes to the Pampalon deprivation (PDI) index. This index is a composite measure of material and social deprivation, used to address health inequalities. It is based on small geographical units, enumeration areas (EA) from the 1991 and 1996 Canadian censuses and dissemination areas (DA) from the 2001, 2006, 2011, and 2016 censuses(138). Quintiles of the material and social deprivation indices were derived by linking the DCC cohort to the 2016 PDI and the ICC cohort with the 2011 PDI using residential postal codes.

Neurodevelopmental Outcome Data

Neurodevelopmental outcome data were obtained from the NFC database. Although the NFC follows infants with GA ≤28 weeks and / or birth weight ≤1250 gram, this study included only those born at GA <29 weeks, as neonatal morbidity correlates more strongly with gestational age than with birth weight. Furthermore, older small-for-gestational-age (SGA) infants typically align developmentally with peers of similar gestational age rather than similar weight. The widespread use of gestational dating ultrasounds, particularly when the last menstrual period was uncertain, further supported the reliability of GA as a predictor of postnatal morbidity.

Throughout the study period, all surviving preterm infants born at GA < 29 weeks were prospectively followed for comprehensive developmental assessments and longitudinal evaluations by a multidisciplinary team comprising physiotherapists, physicians, occupational therapists, psychologists, speech and language pathologists, dietitians, optometrists, and audiologists. Examinations were conducted at 4, 8-, 12-, 18-, and 36-months CA at the NFC, located at Alberta Children's Hospital. Growth parameters, including height, weight and head circumference, were measured using standardised techniques. Neurological and developmental

assessments were conducted independently by neonatologists or pediatricians, certified psychologists, occupational therapists, physiotherapists, dieticians, speech therapists, nurses, audiologists and ophthalmologists. The neurological examination included assessment of tone, strength, reflexes and posture.

Data Management

Following identification from the administrative neonatal database, each eligible participant was assigned a unique study identification number. Regional Health Record Numbers (RHRNs) were temporarily used to link data between the neonatal database at FMC and the NFC database.

Each variable from the dataset was entered, coded and saved in Microsoft Excel 365 prior to editing. Variables defined as “no” were coded as 0 and those defined as “yes” were coded as 1. After verification, the coded data were imported into Stata BE version 18.5 for statistical analysis.

Study Variables

Outcome Variables:

The main outcome variables were divided into two subcategories: long-term neurodevelopmental outcomes and short-term neonatal outcomes.

Long-term neurodevelopmental outcome variables *(18 - 24 months and 36 months corrected age)*

- Death or any NDI (neurodevelopmental impairment)
- death or severe NDI
- any NDI
- severe NDI
- cerebral palsy

- cognitive delay
- motor delay
- language delay
- visual impairment
- hearing impairment
- growth (height, weight and head circumference, continuous variable)

Short-term neonatal outcome variables

RDS, BPD, PDA, surgically treated PDA, neonatal sepsis, IVH, severe IVH (grade 3 or 4), PVL, SNI (IVH ≥ grade III and/or PVL), NEC (> stage ii), ROP, severe ROP (≥ stage III± treatment), discharge home on oxygen, number of packed red cell / whole blood transfusions, duration of mechanical ventilation, duration of non-invasive respiratory support, duration of oxygen support and length of NICU stay (days).

Exposure Variables:

The exposed group consisted of preterm infants born at GA < 29 weeks between 1 July 2012, and 31 December 2017, who received DCC at birth.

The unexposed group consisted of preterm infants born at GA < 29 weeks between 1 January 2006, and 31 December 2011, and who received ICC at birth.

Maternal Variables

- Maternal age at delivery (years, continuous variable)
- Completion of high school (yes or no)
- Pregnancy induced hypertension (PIH) (yes or no)
- Gestational diabetes (yes or no)
- Chorioamnionitis (Clinical and or histopathological confirmed) (yes or no)
- Mode of delivery (caesarean section versus vaginal delivery)
- Use of antenatal corticosteroids (ANCS) (yes or no)

- Use of antibiotics during labor and delivery (yes or no)
- Parity (multiparous or nulliparous)
- Multiple birth (twins/triplets/greater versus singleton)
- Prolonged rupture of membrane (PROM ≥24 hours) (yes or no)
- Smoking during pregnancy (yes or no)
- Use of alcohol during pregnancy (yes or no)
- Socio-economic status by Pampalon deprivation index

Neonatal Variables

- Gestational age at birth (GA) (weeks, continuous variable)
- Birth weight (grams, continuous variable)
- Sex (male or female)
- Small for gestational age (SGA, $<10^{th}$ centile weight for that GA) (yes or no)
- Apgar scores at 5 minutes <7
- Number of packed red cells /whole blood transfusion (times, continuous variable)
- Duration of mechanical ventilation (days, continuous variable)
- Duration of non-invasive respiratory support (days, continuous variable)
- Duration of Oxygen (days, continuous variable)
- Length of stay at NICU (days, continuous variable)

Data Analysis

All statistical tests were two sided and the significance level was specified as $\alpha=0.05$.

Descriptive Statistics

Descriptive statistics were used to characterize the study population. Categorical variables were summarized using frequency and percentage, whereas continuous variables were described using mean (standard deviation) or median (interquartile range), depending on the data distribution.

Univariate and Bivariate Analysis

Univariate analysis was conducted first to describe and summarize variable distributions. Associations between the independent variable (DCC as exposure) and dependent variables (outcomes) were examined using bivariate analysis. A similar approach was used to analyze the association between DCC and neurodevelopmental outcomes (death or NDI, death or severe NDI, any NDI, severe NDI, and each of the four components: cerebral palsy, cognitive, motor, and language delay, visual and hearing impairment). The independent Student's t-test was used to compare normally distributed continuous variables, whereas the Mann-Whitney U test was used for non-normally distributed data. Categorical outcomes were compared using the chi square test or Fisher's exact test when the expected cell frequency was <5 in some cells.

The primary outcome was defined as a composite of death or any NDI assessed at 18–24 months and 36 months corrected age. The outcome variable was coded as 0 if neither death nor NDI occurred and as 1 if either—death or any form of NDI—was identified at follow-up.

To ensure the accuracy and comparability, infants who died or showed signs of NDI without a confirmed diagnosis of cerebral palsy, cognitive delay, motor delay, language delay, hearing impairment, or visual impairment were excluded. This criterion ensured consistency in outcome definitions and to reduce the risk of misclassification.

Multivariable Analysis

The potential influence of maternal and neonatal factors as effect modifiers or confounders on the association between DCC and neurodevelopmental outcomes was evaluated using Mantel-Haenszel test (139) and logistic regression analysis (140).

The Mantel-Haenszel test compared between stratum specific odds ratios (ORs) for each variable to detect effect modification and between crude ORs and adjusted ORs to identify confounding effects. A p-value < 0.05 indicated that a variable functioned as an effect modifier. When non-significant, a ≥10% change between the crude and the Mantel-Haenszel (M-H) adjusted ORs was used as the threshold for identifying confounding, with consideration also given to clinical relevance (141).

Initially, covariates showing statistically significant differences (p <.05) between the DCC and ICC groups were identified as potential confounders. Variable selection was guided by both statistical significance and the magnitude of change between crude and adjusted ORs. A covariate was included in the model if its addition altered the effect estimate by ≥ 10%. Variables previously identified as confounders in existing literature were also prioritised to minimise residual confounding. Multicollinearity Assessment was done using the matrix of correlation to identify if independent variables were highly correlated. With multicollinearity, it is hard to determine the true effect of each independent variable on the dependent variable and results in less reliable model. Moreover, clinically relevant variables were prioritized for retention in the final regression model.

Logistic regression analysis began by testing for effect modification through inclusion of interaction terms (exposure × covariate) for variables identified as potential effect modifiers in stratified analysis. Covariates with statistically significant interaction terms (p < 0.05) were treated as effect modifiers, while non-significant interaction terms were excluded from the final model.

Each final logistic regression model for neurodevelopmental outcomes was evaluated for goodness of fit using the Hosmer-Lemeshow test (142), recognising that separate neonatal cohorts were analysed for the DCC and ICC periods. The final models estimated the effect of DCC on neurodevelopmental outcomes, adjusting for covariates with plausible clinical or statistical associations. This modelling process was applied independently to all outcome measures assessed at 18–24 months and 36 months corrected age. Propensity score matching (143) was conducted to align participants with similar confounder distributions, providing unbiased estimates of exposure effect. Propensity scores were calculated using a multivariable logistic regression model that included GA at birth, male sex, caesarean section (C-section), and ANCS as covariates. Matching was conducted in Stata BE version 18.5 using a caliper width equal of 0.2 times the standard deviation of the logit-transformed propensity scores, with outliers outside this range excluded from the matched sample. Odds ratios with 95% confidence intervals and two-sided p- values were calculated to demonstrate associations.

Ethical Considerations

This study was approved by the CHREB of the University of Calgary. Following ethical approval, permission to use administrative data for research purposes was obtained from Alberta Health Services, and the NFC, Section of Neonatology. Human participants were not directly involved as the health outcome databases of preterm infants admitted to the FMC and followed at the NFC, were assessed retrospectively. Accordingly, a waiver of consent was sought to access data from existing records. This was justified because no intervention was conducted, the outcomes had already occurred, retrospective consent was not feasible, there was no additional risk to infants whose data were analysed and there was no justification for contacting families. Each infant was assigned a unique study identification (ID) number to ensure accurate data

management. These identifiers were stored in a separate secure file with restricted access limited to the investigators. Identifying information was removed from the database and all data were stored on the AHS network in a password- protected file to maintain confidentiality. Data analysis was performed anonymously, and results were reported without identifying any individual infant.

Operational Definitions

Deferred Cord Clamping (DCC): Deferred cord clamping refers to the practice of clamping the umbilical cord at least ≥ 15 seconds (64) and it may be continued up to 3–5 minutes or until the umbilical cord stop pulsating (21, 40).

Immediate Cord Clamping (ICC): Immediate cord clamping is defined as the clamping of the umbilical cord <15 seconds after delivery (64).

Physiological-Based Cord Clamping (PBCC): Physiological-based cord clamping is defined as keeping the umbilical cord intact after birth until the newborn has achieved lung aeration and demonstrates respiratory stability—evidenced by regular spontaneous breathing, a heart rate 100 beats per minute or above, and oxygen saturation greater than 90%, while receiving less than 40% supplemental oxygen (44).

Umbilical Cord Milking (UCM): Umbilical cord milking is defined as manually expressing 20–30 cm of the umbilical cord blood toward the newborn by gently squeezing the cord three to five times at an approximate rate of 10 cm per second. This technique can be performed with the cord intact (intact UCM or I-UCM), or after the cord has been cut and separated from the placenta (cut UCM) (47).

Gestational Age (GA): Gestational age is defined as the number of completed weeks that have elapsed between the first day of the mother's last menstrual period and the day of delivery (144). It is the best obstetric estimate, which incorporates early prenatal ultrasound findings and obstetric history, unless the postnatal pediatric assessment—based on the Ballard scoring system—differed by more than two weeks. The Ballard score evaluates gestational age through an assessment of the newborn's neuromuscular (posture, square window, arm recoil, popliteal angle, scarf sign, heel to ear) and physical maturity (skin, lanugo, plantar surface, breast, eye / ear, genitals) across six criteria in each domain (145).

Corrected age (CA): Corrected age is determined by subtracting the number of weeks of prematurity (i.e., the difference between 40 weeks and the gestational age at birth) from the infant's chronological age. It is typically used for assessing growth and developmental milestones in preterm infants up to 3 years of age (144).

Post menstrual age (PMA): Postmenstrual age refers to the time elapsed between the first day of the mother's last menstrual period (LMP) and the current date or the date of assessment (time passed after birth) of the infant. It is used for premature and newborn infants' developmental or medical assessment (144).

Small for gestational age (SGA): Small for gestational age is defined as birth weight below the 10th percentile for that gestational age, based on the Fenton growth chart for preterm infants (146).

Appropriate for gestational age (AGA): Appropriate for gestational age is defined as birth weight between the 10th and the 90th percentile for that gestational age based on the Fenton growth chart for preterm infants (146).

Respiratory Distress Syndrome (RDS): Respiratory distress syndrome is a common breathing disorder that often occurs in preterm infants (born before 30-32 weeks gestation) due to lack of surfactant. Symptoms include rapid breathing (respiratory rate > 60 breaths per minute), nasal flaring with each breath, intercostal, subcostal and sternal retractions, expiratory grunting, cyanosis, diminished breath sounds along with characteristic chest x-ray findings. This condition requires treatment with nasal continuous positive airway pressure (nCPAP) and / or surfactant replacement as well as mechanical ventilation when necessary (147).

Bronchopulmonary dysplasia (BPD): Bronchopulmonary dysplasia is defined as the need of additional oxygen at 36 weeks PMA in premature infants born at ≤30 weeks gestational age (148).

Patent ductus arteriosus (PDA): Patent ductus arteriosus refers to the continued patency of the fetal shunt between the pulmonary artery and the aorta. Under normal conditions, this ductus functionally closes within the first 72 hours after birth; however, delayed closure is observed in up to 80% of infants born between 25 and 28 weeks of gestation. It can lead to pulmonary over circulation and systemic hypoperfusion, potentially contributing to significant morbidity in preterm infants. The approach to PDA treatment has recently shifted from advocating an aggressive and early closure to watchful observation. The timing of spontaneous closure is inversely proportional to GA, with a median duration of approximately 71 days in infants born at <26 weeks, compared to 6 days in those born at ≥30 weeks. Usually, it was treated medically (indomethacin or ibuprofen or acetaminophen) or surgically or both (81, 149).

Neonatal Sepsis: Neonatal sepsis is a systemic infection, defined by isolation of a pathogenic organism from a sterile site, typically blood or cerebrospinal fluid, in a symptomatic infant.

Sepsis is commonly classified based on the timing of symptom onset into two categories: early-onset sepsis (EOS), which manifests within the first 72 hours of life and is caused by bacterial pathogens transmitted vertically from mother to infant before or during delivery while late-onset sepsis (LOS) occurs after 72 hours of age and may be caused by vertically or horizontally acquired pathogens (85).

Intraventricular Haemorrhage (IVH): Intraventricular hemorrhage means bleeding into the ventricular system of the brain due to rupture of the germinal matrix. It typically occurs in premature infants born between 23 and 32 weeks of gestation, often because of sudden fluctuations in blood flow. IVH was originally classified using the Papile et al. criteria, based on head CT scan. However, cranial ultrasound has now become the standard diagnostic tool, especially in extremely preterm infants admitted to the NICU, where it is routinely performed during the first week of life for early detection. IVH is categorized by severity, Grade I: subependymal (germinal matrix) hemorrhage only, Grade II: IVH without ventricular dilatation, Grade III: IVH with ventricular dilatation, Grade IV: IVH with ventricular dilatation and extension into the brain parenchyma (periventricular hemorrhagic infarction) (150).

Severe intraventricular Haemorrhage (severe IVH): Severe intraventricular hemorrhage refers to Grade III or Grade IV IVH, as classified by the Papile grading system. Grade III IVH involves significant bleeding into the ventricular system with acute ventricular dilation, while Grade IV IVH (also referred to as periventricular hemorrhagic infarction) includes parenchymal involvement due to venous infarction adjacent to the ventricles (151).

Periventricular Leukomalacia (PVL): Periventricular leukomalacia is a brain injury seen in premature infants, involving damage to the white matter surrounding the ventricles of the brain.

It results from decreased oxygen or blood supply and appears as localized tissue death in the periventricular region. Diagnosis is typically made using cranial ultrasound or MRI (152).

Severe neurological injury (SNI): Severe neurological injury is defined as grade 3 or 4 IVH and / or PVL diagnosed using a cranial ultrasound scan or magnetic resonance imaging (153).

Necrotising Enterocolitis (NEC): Necrotising Enterocolitis is a life-threatening condition characterized by inflammation and bacterial invasion of the intestine, which can cause necrosis of the intestinal tissue. It is classified according to Modified Bell's Criteria: stage I (suspected): supportive care is provided, and diagnostic evaluation is performed to exclude other causes, stage II (definite NEC): management by nasogastric decompression, intravenous fluids, and broad-spectrum antibiotics, stage III (advanced NEC): requires urgent surgical intervention (111).

Retinopathy of prematurity (ROP): Retinopathy of prematurity is a condition involving abnormal blood vessel growth in the retina, primarily affecting extremely premature infants who have received high levels of oxygen therapy. Diagnosis is performed by an ophthalmologist using the criteria set out in the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3) (154).

Severe retinopathy of prematurity (sROP): Retinopathy of prematurity is classified as severe when it reaches Stage 3 or higher. Treatment for severe ROP typically involves laser therapy or injection of anti-VEGF medications to halt abnormal vessel growth, and may require surgical procedures like scleral buckling or vitrectomy to reattach the retina (155).

Definition of Neurodevelopmental Outcome Variables:

Neurodevelopmental impairment (NDI): Neurodevelopmental impairment includes presence of any of the following outcomes: cerebral palsy, GMFCS ≥1; cognitive, motor or language delay, Bayley Scales of Infant Development, 3rd edition (BSID-III) scores of <85 on any component (cognitive, motor, language composite score at 18-24 months) or full scale IQ (FSIQ) <85 on the Wechsler Preschool and Primary Scale of Intelligence, 3rd or 4th edition (WPPSI-III or IV) at 36 months or >1SD below the mean; sensorineural hearing loss or auditory neuropathy with or without aid; visual impairment with corrected visual acuity of >20/60 in the better eye, or unilateral / bilateral blindness(156). The Leiter-R (Leiter international performance scale-revised) test is a non-verbal intelligence test suitable for non-English-speaking children. It has a mean of 100 and standard deviation of 15, consistent with WPPSI. Cognitive scores from the Leiter-R were categorized using the same classification scheme applied in the WPPSI assessment (157).

Severe neurodevelopmental impairment (s-NDI): Severe neurodevelopmental impairment includes presence of any of the following outcomes: cerebral palsy, GMFCS ≥3; cognitive, motor or language delay, Bayley Scales of Infant Development, 3rd edition (BSID-III) scores of <70 on any component (cognitive, language, motor composite score 18-24 months) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) iii/iv, scores of <70 (36 months) or >2 SD below the mean ; bilateral sensorineural hearing loss or auditory neuropathy with aid; bilateral blindness (corrected visual acuity <20/200 in better eye) (122).

Cerebral palsy (CP): CP is a heterogeneous group of disorders that can cause spasticity, dystonia, muscle contractures, weakness and coordination difficulty which affects the ability to

control movements. The diagnosis of cerebral palsy was made if the child had non-progressive motor impairment characterized by abnormal muscle tone in at least one extremity leading to functional impairment. Cerebral palsy is diagnosed by neonatologists / pediatricians through a detailed neurological examination, and its severity is classified using the GMFCS (Gross Motor Function Classification System) rating at the time of diagnosis. A physiotherapist is also involved in the assessment of muscle tone and motor function in the clinic (158).

GMFCS I: Able to walk without limitations. Individuals less than two years of age can crawl on hands and knees, pull to stand, cruise when holding onto furniture. They are usually able to attain independent walking between the age of 18 months and two years. Between two and four years of age, can sit and transition between sitting and standing independently.

GMFCS II: Able to walk with limitations. A child before the age of two can sit with upper extremity support, crawl on their stomach, and may be able to pull-to-stand or cruise with support. Between ages 2 and 4, the child can transition into and out of sitting without support, can sit without support (may need to use their upper extremities for balance), can crawl on hands and knees, cruise with support and walk with a mobility device.

GMFCS III: Able to walk with a hand-held mobility device in indoor but use wheeled mobility in the community and for longer distances. Children in GMFCS III who are less than 2 years old can roll and occasionally crawl forward when lying on their stomach, as well as sit with some low back support. Between ages 2 and 4, a child can “W” sit on the floor with some help getting into the position, crawl on his / her stomach or creep on all fours and may pull-to-stand and walk short distances using a handheld mobility device (walker or gait trainer) with some assistance for maneuvering.

GMFCS IV: Able to sit with support, but self-mobility is limited, usually needs transport in a manual wheelchair or using powered mobility. Before the age of 2, children have head control and can roll but require truncal support to sit. Between ages 2 and 4, a child can sit with upper extremity support, require assistance to transition into sitting, and may require adaptive equipment for sitting or standing. At this age, some self-mobility is possible through rolling or stomach crawling for short distances, but reciprocal leg movement is absent.

GMFCS V: Have severe limitations with head and trunk control and self-mobility is only possible using a powered wheelchair. Children before the age of 2 do not have independent head or trunk control and require assistance to roll. Between the ages of 2 to 4, the child has no independent movement and requires assistance for transport using manual mobility devices. Adaptive equipment is required for sitting or standing. It is possible to become independent using power mobility with additional adaptations.

Cognitive delay: Cognitive function was assessed with Bayley Scales of Infant Development, 3rd edition (BSID-III), <85 on cognitive composite score at 18-24 months and FSIQ <85 on the Wechsler Preschool and Primary Scale of Intelligence, 3rd, or 4th edition (WPPSI-III/IV) or >1 SD below the mean, tested by trained healthcare professionals (159). The Leiter-R (Leiter international performance scale-revised) test is a non-verbal intelligence test suitable for non-English-speaking children. It has a mean of 100 and standard deviation of 15, consistent with WPPSI. Cognitive scores from the Leiter-R were categorized using the same classification scheme applied in the WPPSI assessment (157).

Severe cognitive delay means Bayley Scales of Infant Development, 3rd edition (BSID-III), scores of <70 on cognitive component (cognitive composite score 18-24 months) or the Wechsler

Preschool and Primary Scale of Intelligence (WPPSI) III/IV, scores of <70 (36 months) or >2 SD below the mean (159, 160).

In this study, cognitive assessments at 18–24 months were conducted using BSID-III for both the DCC and ICC cohorts. However, at 36 months CA, cognitive outcomes were assessed using the WPPSI-IV in the DCC cohort and the WPPSI-III in the ICC cohort. Because these instruments differ in their structure, scoring systems, normative data, and test content, any observed differences in cognitive performance between the cohorts may reflect variations in the assessment tools rather than true differences in developmental outcomes. This discrepancy introduces the potential for measurement bias.

Motor / Language delay: According to the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III), a mild delay is indicated when the motor or language composite score is <85, while a severe delay is defined as a score <70, typically assessed at 18 to 24 months of age (159).

Growth: The Fenton growth chart is used for detecting SGA among preterm infants. The WHO growth standard is used for measuring growth parameters at 18-24 months and 36 months corrected age (146, 161).

Bilateral hearing loss: Sensorineural hearing loss requiring amplification (159).

Bilateral blindness: Blindness is defined as visual acuity <20/200 following refractive correction in the strongest eye (159).

Pampalon Deprivation Index: The Pampalon deprivation index (PDI) is a composite measure of material and social deprivation, used to address health inequalities in rural and vulnerable

populations to access health care services. Socioeconomic status was assessed using the Pampalon material and social deprivation index to classify the study cohort into quintiles of deprivation, It was based on small geographical units, the enumeration areas (EA) from the 1991 and 1996 Canadian censuses and the dissemination areas (DA) from the 2001, 2006, 2011, and 2016 censuses which can be linked to the administrative databases by residential postal codes. The deprivation index was built from six socioeconomic indicators: the proportion of the population aged 15 years or older without a high school diploma or equivalent education, employment to population ratio, average income, living alone, separated, divorced, or widowed and single parents. These indicators were combined to create a factor score for each EA or DA. The distribution of EA / DAs was then divided into five quintiles, with quintile 1 denoting the most privileged EAs / DAs and quintile 5 representing the population residing in the most deprived EAs / DAs. The index was calculated separately for material and social component. The material Deprivation Index reflects the deprivation of goods and conveniences (average household income; unemployment rate; and high school education rate). The social Deprivation Index reflects the deprivation of relationships among individuals in the family, the workplace, and the community (proportion of the population separated, divorced, or widowed; proportion of the population that lives alone; and proportion of the population that has moved in the past five years). Here the residential postal codes for mothers in the DCC group were linked with the 2016 Pampalon deprivation index and those for the ICC groups were linked with the 2011 Pampalon deprivation index (138).

CHAPTER THREE: RESULTS

This chapter is organized to first describe the process of sample selection, followed by a detailed presentation of maternal and neonatal characteristics among infants exposed to deferred cord clamping (DCC) and immediate cord clamping (ICC). It then examines the differences in short-term neonatal morbidities, summarizes the variations in long-term neurodevelopmental outcomes between the two groups, and concludes with a comparative analysis of the infants who received DCC versus ICC, during the designated DCC implementation period.

Descriptive Statistics

Flow of Study Sample Selection

A total of 1384 preterm infants, born at <29 weeks' gestation were admitted to the regional neonatal intensive care unit (NICU) at Foothills Medical Centre (FMC) in Calgary, Alberta, between 1 January 2006, and 31 December 2017. Preterm infants born between 1 January 2006 and 31 December 2011 (**period 1**), who received ICC, were included in the ICC group (unexposed). Those born between 1 July 2012 and 31 December 2017 (**period 2**), who received DCC, were included in the DCC group (exposed). A six month wash out period (1 January to 30 June 2012) was applied between the two groups.

From 1384 infants, 981 met the inclusion criteria for this study; A total of 403 were excluded for various reasons: 49 were born during washout period, 1 had chromosomal anomalies, 83 had congenital anomalies and 270 were born to mothers with antepartum haemorrhage. The exclusion criteria were included conditions such as chromosomal anomalies, congenital anomalies and antepartum haemorrhage as these were independently associated with perinatal mortality, morbidities, neurodevelopmental impairments as well as poor growth (162-164).

After applying the inclusion and exclusion criteria, a total of 540 preterm infants were included in the DCC time-period. Of these, 241 infants lacked documented information regarding type of cord clamping administered at birth. Additionally, to mitigate "healthy worker effect" and minimize selection bias, infants born during the DCC period who received ICC due to immediate need for neonatal resuscitation or critical conditions of mothers (n=134) were excluded from the study sample (133). As a result, the final DCC cohort comprised 165 infants, representing 30.56% of the initial DCC sample (165 out of 540 infants). For comparison, the ICC cohort included 441 infants, constituting 100% of the original ICC sample.

Overall, follow-up data were unavailable for 39 preterm infants at 18–24 months follow-up (including 12 from the DCC group and 27 from the ICC group), and for 46 preterm infants at 36 months follow-up (including 8 from the DCC group and 38 from the ICC group).

Two analytical datasets were generated to conduct the analyses. The first dataset comprised 153 preterm infants in DCC group (including 11 deaths and 142 with available follow-up data) and 414 preterm infants in ICC group (including 29 deaths and 385 with follow-up data), all of whom had outcome data available at 18-24 months corrected age (**Figure 2**).

The second dataset included 134 preterm infants in the DCC group with available follow-up data and a total 11 deaths (0 at 36 months and 11 between 18–24 months). For comparison, the ICC cohort included 346 infants with follow-up data and a total of 30 deaths (1 at 36 months and 29 between 18–24 months), all of whom had data available for analysis at 36 months (**Figure 2**).

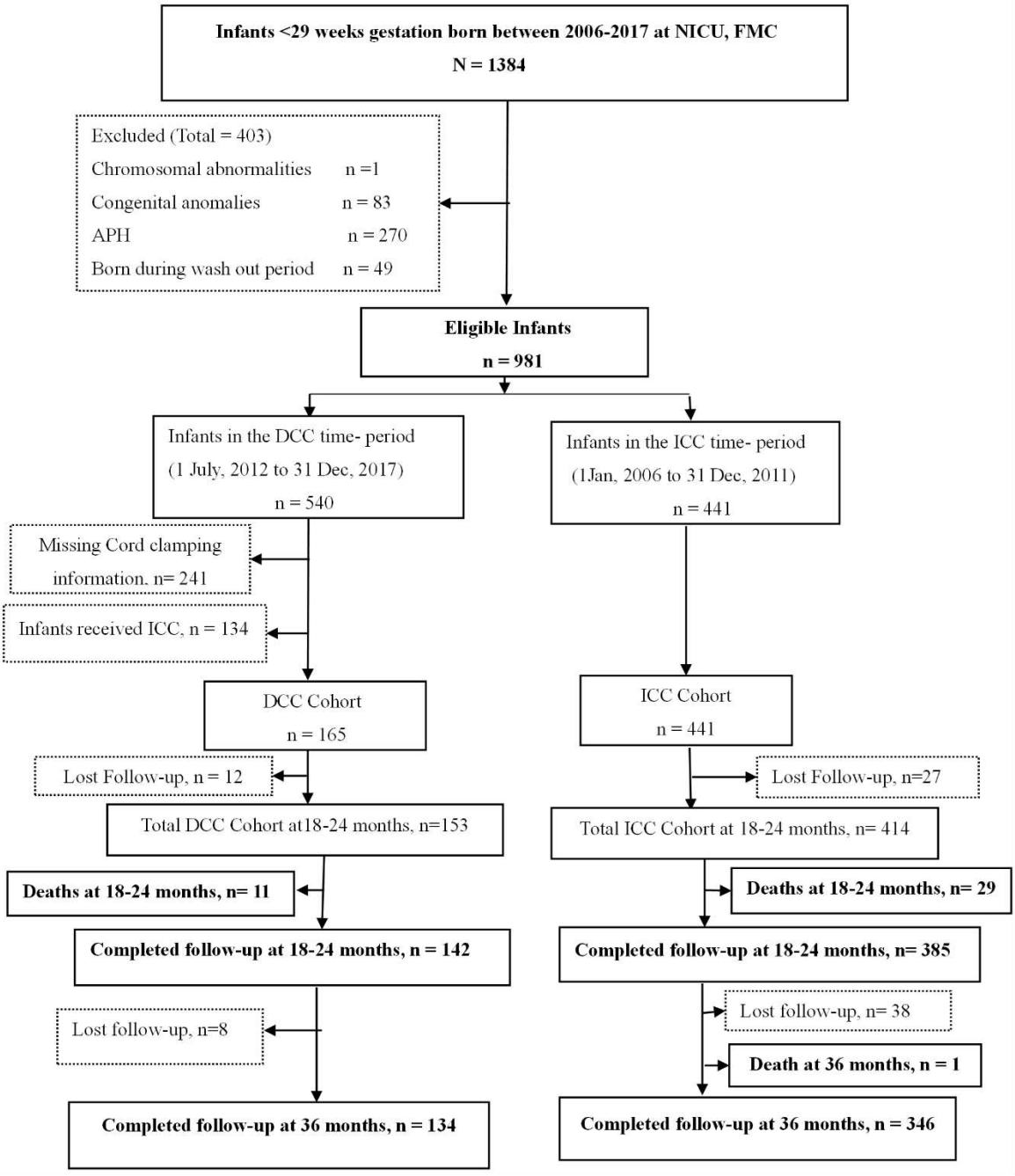

Figure 2. Flow diagram of the study cohort.

All discrete variables were dichotomized, with a value of 0 indicating absence and 1 indicating the presence of the respective condition. This binary coding approach was consistently applied to all short-term and long-term neurodevelopmental outcome variables. Statistical comparisons

were conducted using two-sided t-test for normally distributed continuous variables, Mann-Whitney U test for continuous variables that were not normally distributed. Categorical variables were assessed using the Chi-squared test and the Fisher's exact test was employed when expected cell counts were less than 5.

Maternal Characteristics

This section provides a detailed overview of the maternal characteristics of infants included in the two groups. Variables were selected based on previous literature on maternal morbidities and developmental outcomes in preterm infants. The aim was to examine the maternal demographic characteristics as potential factors to short-term neonatal morbidities in those who received DCC, as well as their influence on mortality, long-term neurodevelopmental outcomes, and growth.

Maternal Age at Delivery

Maternal age data were available for all 606 (100%) preterm infants. The distribution of maternal age at the time of birth for DCC and ICC cohorts is illustrated in **Figure 3**.

The maternal age distribution was slightly skewed in both groups due to presence of outliers. The median maternal age was 33 years (IQR: 28–38) in the DCC group and 30 years (IQR: 25–34) in the ICC group. Mann-Whitney U test was performed, revealing that mothers in the DCC group were significantly older than those in ICC group (33 vs 30 years, $p = < .001$).

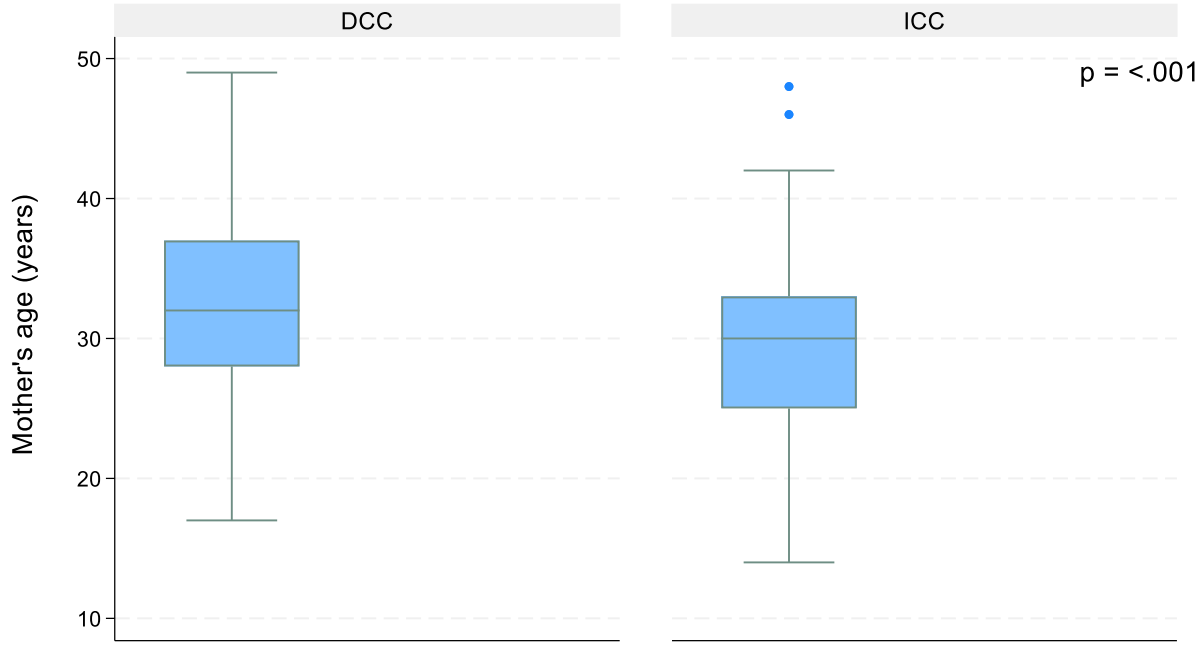

Figure 3. Box plots of maternal age for the DCC and ICC groups. The line in the middle of the box represents the median. The lower and upper borders of the boxes represent lower or 1st quartile (Q1) and upper or 3rd quartile (Q3). The lower and upper whiskers represent the 95% CI. The dots represent the outliers. All these would apply to later boxes as well.

Completion of High School

Data on maternal education status were available for 506 (83.50%) infants. The proportion of mothers who had completed a high school degree was similar between two groups (87.5% vs 85.71%; p = .613), (**Table 1**).

Table 1. Comparison of high school completion among mothers in DCC and ICC groups

Completed high school	**DCC Group (n = 128)**	**ICC group (n = 378)**	**p-value***
Yes, n (%)	112 (87.50)	324 (85.71)	.613
No, n (%)	16 (12.50)	54 (14.29)	

*p-value obtained using Chi-squared test

Pregnancy Induced Hypertension (PIH)

Data on the presence of PIH in mothers were available for 495 (81.68%) infants. The proportion of mothers with PIH was 20% in the DCC and 17.58% in the ICC groups. This difference was not statistically significant (p = .512), (**Table 2**).

Table 2. Comparison of mothers with PIH in DCC and ICC groups

PIH	**DCC Group (n = 165)**	**ICC Group (n = 330)**	**p-value***
Yes, n (%)	33 (20)	58 (17.58)	.512
No, n (%)	132 (80)	272 (82.42)	

*p-value obtained using Chi-squared test
PIH: pregnancy induced hypertension

Gestational Diabetes

Data on maternal gestational diabetes were available for 495 (81.68%) infants. The proportion of mothers with gestational diabetes was similar between the two groups (8.48% in the DCC group vs 5.45% in the ICC group; p = .196), (**Table 3**).

Table 3. Comparison of mothers with gestational diabetes in DCC and ICC groups

Gestational Diabetes	**DCC Group (n = 165)**	**ICC Group (n = 330)**	**p-value***
Yes, n (%)	14 (8.48)	18 (5.45)	.196
No, n (%)	151 (91.52)	312 (94.55)	

*p-value obtained using Chi-squared test

Clinical and Histopathological Chorioamnionitis

Clinical chorioamnionitis is diagnosed based on maternal signs and symptoms, including maternal fever accompanied by one or more of the following: maternal tachycardia, fetal tachycardia, uterine tenderness, foul-smelling amniotic fluid, and maternal leukocytosis, as assessed by obstetric team. In contrast, histopathological chorioamnionitis was confirmed

through microscopic examination of placental and membrane tissues, characterized by neutrophilic infiltration of the chorion and /or amnion (indicating a maternal inflammatory response). In more advanced cases, inflammation of the umbilical cord (funisitis) or chorionic plate vessels (reflecting a fetal inflammatory response) may be observed. Data were available for 583 (96.20%) infants. The proportion of mothers diagnosed with chorioamnionitis was similar between the two groups (21.82% vs 25.12%; p = .402), (**Table 4**).

Table 4. Comparison of mothers who had Chorioamnionitis in DCC and ICC groups

Chorioamnionitis	**DCC Group (n = 165)**	**ICC Group (n = 418)**	**p-value***
Yes, n (%)	36 (21.82)	105 (25.12)	.402
No, n (%)	129 (78.18)	313 (74.88)	

*p-value obtained using Chi-squared test

Mode of Delivery

Data on mode of delivery were available for 606 (100%) infants. The proportion of mothers who delivered via caesarean section was not statistically different between the two groups (52.73% vs 58.50%; p = .201), (**Table 5**).

Table 5. Comparison of caesarean delivery among mothers in DCC and ICC cohorts

Caesarean Section	**DCC Group (n = 165)**	**ICC Group (n = 441)**	**p-value***
Yes, n (%)	87 (52.73)	258 (58.50)	.201
No, n (%)	78 (47.27)	183 (41.50)	

*p-value obtained using Chi-squared test

Antenatal Corticosteroids (ANCS)

Pregnant women at risk of premature delivery, were administered ANCS (betamethasone or dexamethasone) to accelerate fetal lung maturation. Data were available for 602 (99.34%) infants. The proportion of ANCS administration differed significantly between the groups; (93.94% vs 85.35%, p = .004); (**Table 6**).

Table 6. Comparison of use of antenatal corticosteroids in DCC and ICC cohorts

Antenatal Corticosteroids	**DCC Group (n = 165)**	**ICC group (n = 437)**	**p-value***
Given, n (%)	155 (93.94)	373 (85.35)	.004[a]
Not Given, n (%)	10 (6.06)	64 (14.65)	

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

Use of Antibiotics During Labor and Delivery

Data on the antibiotics use were available for 599 (98.84%) infants. Statistical difference was observed in the proportion between groups (70.30% vs 61.06 %, p = .036), (**Table 7**).

Table 7. Comparison of use of maternal antibiotics in DCC and ICC groups

Antibiotics at Labour	**DCC group (n = 165)**	**ICC Group (n = 434)**	**p-value***
Yes, n (%)	116 (70.30)	265 (61.06)	.036[a]
No, n (%)	49 (29.70)	169 (38.94)	

*p-value obtained using Chi-squared test
[a]Indicates statistical significance

Parity

Parity denotes the number of births (including live births and still births) where pregnancies reached viable gestational age or foetal weight (≥20 weeks' gestation or ≥400 grams birthweight)

(165). Data were available for 590 (97.36%) infants. Parity was coded as 0 for nulliparous and 1 for multiparous. The proportion of multiparous mother was similar between the groups (49.09% vs 44.94%; p = .364). The Graphic and numeric comparison of parity in both cohorts is shown in **Figure 4** and **Table 8**.

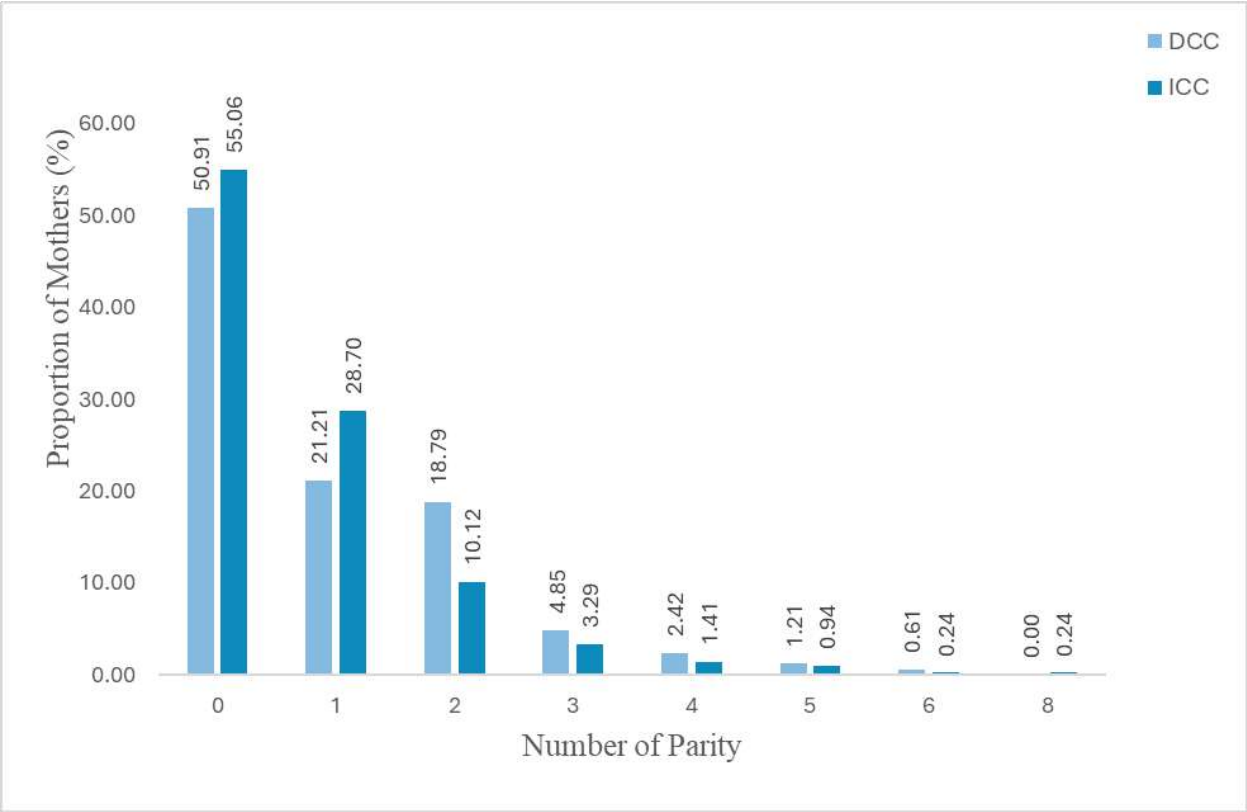

Figure 4. Bar diagrams showing distribution of parity in DCC & ICC cohorts.

Table 8. Comparison of mothers' parity in DCC and ICC cohorts

Parity	**DCC Group (n = 165)**	**ICC Group (n = 425)**	**p-value***
Multiparous, n (%)	81 (49.09)	191 (44.94)	.364
Nulliparous, n (%)	84 (50.91)	234 (55.06)	

*p-value obtained using Chi-squared test

Multiple Birth

Data on multiple birth were available for all 606 (100%) infants. The proportion of multiple births was similar between the DCC and ICC groups (27.27 vs 32.43%; p = .222), (**Table 9**). In the DCC group, there were 41 twin births and 4 were triplet births, while in the ICC group, there were 112 twin births and 31 were of triplet births.

Table 9. Comparison of multiple birth status in DCC and ICC cohorts

Multiple Birth	**DCC Group (n = 165)**	**ICC group (n = 441)**	**p-value***
Yes, n (%)	45 (27.27)	143 (32.43)	.222
No, n (%)	120 (72.73)	298 (67.57)	

*p-value obtained using Chi-squared test

Prolonged Rupture of the Membrane (PROM, ≥ 24 hours)

Data on PROM were available for 601 (99.17%) infants. Membrane rupture occurring < 24 hours before delivery was coded as 0 while rupture occurring at or beyond 24 hours was coded as 1. The proportion of PROM was similar between the DCC and ICC groups (29.70% vs 25.92%; p = .351); (**Table 10**).

Table 10. Comparison of PROM (≥24 hours) among mothers in DCC and ICC cohort

PROM	**DCC Group (n = 165)**	**ICC group (n = 436)**	**p-value***
Yes, n (%)	49 (29.70)	113 (25.92)	.351
No, n (%)	116 (70.30)	323 (74.08)	

*p-value obtained using Chi-squared test
PROM: prolonged rupture of the membrane

Smoking During Pregnancy

The data on maternal smoking were available for 603 (99.50%) infants. The proportion mothers who smoked was significantly different between DCC and ICC groups (9.70% vs 23.97%; p <.001); (**Table 11**).

Table 11. Comparison of mother's smoking status in DCC and ICC cohorts

Smoking	**DCC Group (n = 165)**	**ICC group (n = 438)**	**p-value***
Yes, n (%)	16 (9.70)	105 (23.97)	< .001[a]
No, n (%)	149 (90.30)	333 (76.03)	

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

Use of Alcohol During Pregnancy

Data on maternal alcohol consumption were available for 602 (99.34%) infants. The proportion was similar between the DCC and ICC groups (4.85% vs 5.03%; p = .926), (**Table 12**).

Table 12. Comparison of alcohol consumption among mothers in DCC and ICC cohorts

Alcohol consumption	**DCC Group (n = 165)**	**ICC group (n = 437)**	**p-value***
Yes, n (%)	8 (4.85)	22 (5.03)	.926
No, n (%)	157 (95.15)	415 (94.97)	

*p-value obtained using Chi-squared test

Socio-economic Status by Pampalon Deprivation Index

Residential postal codes for mothers in the DCC group were linked to the 2016 Pampalon deprivation index whereas those in the ICC group were linked to the 2011 Pampalon deprivation index (138).

Data on maternal socio-economic status were available for 555 (91.58%) infants. Mothers in quintile 5 of both the material and social deprivation quintiles were considered the most materially and socially deprived whereas, those belonged to quintile 1 were considered the most materially and socially privileged.

The proportions of mothers differed significantly between the groups according to the material deprivation quintiles (p = .038); (**Table 13**), while the proportions were similar according to the social deprivation quintiles (p = .261); (**Table 14**).

Table 13. Comparison of mothers in DCC and ICC groups by Material Deprivation Quintiles

Material Deprivation Quintiles	**DCC Group (n = 158)**	**ICC Group (n = 397)**	**p-value**
Q1 (most privileged), n (%)	27 (17.09)	61 (15.37)	
Q2, n (%)	33 (20.88)	70 (17.63)	
Q3, n (%)	30 (18.99)	70 (17.63)	.038[a]
Q4, n (%)	17 (10.76)	89 (22.42)	
Q5(most deprived), n (%)	51 (32.28)	107 (26.95)	

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

Table 14. Comparison of mothers in DCC and ICC cohorts by Social Deprivation Quintiles

Social Deprivation Quintiles	**DCC Group (n = 158)**	**ICC Group (n = 397)**	**p-value**
Q1 (most privileged), n (%)	27 (17.09)	63 (15.87)	
Q2, n (%)	34 (21.52)	61 (15.37)	
Q3, n (%)	32 (20.25)	75 (18.89)	.261
Q4, n (%)	36 (22.79)	97 (24.43)	
Q5(most deprived), n (%)	29 (18.35)	101(25.44)	

*p-value obtained using Chi-squared test

Maternal Baseline Characteristics

Table 15 reflects the maternal baseline characteristics of preterm infants who received either, DCC or ICC at birth.

Table 15. Maternal baseline characteristics of infants received DCC and ICC (N = 606).

Maternal Characteristics	DCC Group (n = 165)	ICC Group (n = 441)	p-value*
Age in years, median (IQR)	33 (28–38)	30 (25–34)	< .001[a]
Completed high school	112/128 (87.50)	324/378 (85.71)	.613
PIH	33/165 (20)	58/330 (17.58)	.512
Gestational Diabetes	14/165 (8.48)	18/330 (5.45)	.196
Chorioamnionitis	36/165 (21.82)	105/418 (25.12)	.402
C-section	87/165 (52.73)	258/441 (58.50)	.201
ANCS	155/165 (93.94)	373/437 (85.35)	.004[a]
Maternal Antibiotics	116/165 (70.30)	265/434 (61.06)	.036[a]
Multiparous	81/165 (49.09)	191/425 (44.94)	.364
Multiple Birth	45/165 (27.27)	143/441 (32.43)	.222
PROM	49/165 (29.70)	113/436 (25.92)	.351
Smoking	16/165 (9.70)	105/438 (23.97)	< .001[a]
Alcohol use	8/165 (4.85)	22/437 (5.03)	.926
Material Deprivation Quintiles			
Quintile1 (most privileged)	27/158 (17.09)	61/397 (15.37)	.038[a]
Quintile 2	33/158 (20.88)	70/397 (17.63)	
Quintile 3	30/158 (18.99)	70/397 (17.63)	
Quintile 4	17/158 (10.76)	89/397 (22.42)	
Quintile 5 (most deprived)	51/158 (32.28)	107/397 (26.95)	
Social Deprivation Quintiles			
Quintile1(most privileged)	27/158 (17.09)	63/397 (15.87)	.261
Quintile2	34/158 (21.52)	61/397 (15.37)	
Quintile3	32/158 (20.25)	75/397 (18.89)	
Quintile4	36/158 (22.79)	97/397 (24.43)	
Quintile5 (most deprived)	29/158 (18.35)	101/397 (25.44)	

*Mann-Whitney test for continuous variables and Chi-squared test for categorical variables.
[a] Indicates statistical significance
Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise
The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroids; C-section: caesarean section; DCC: deferred cord clamping; ICC: immediate cord clamping; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the membrane

Mothers in the DCC group were older, more likely received ANCS and antibiotics, higher proportion lived in the most materially deprived dissemination areas. Conversely, fewer mothers in the DCC group reported smoking.

Neonatal Characteristics

Gestational Age at Birth (GA)

Data on gestational age were available for all 606 (100%) infants**. Figure 5 and 6** describes the proportion and distribution of gestational age in the DCC and ICC groups.

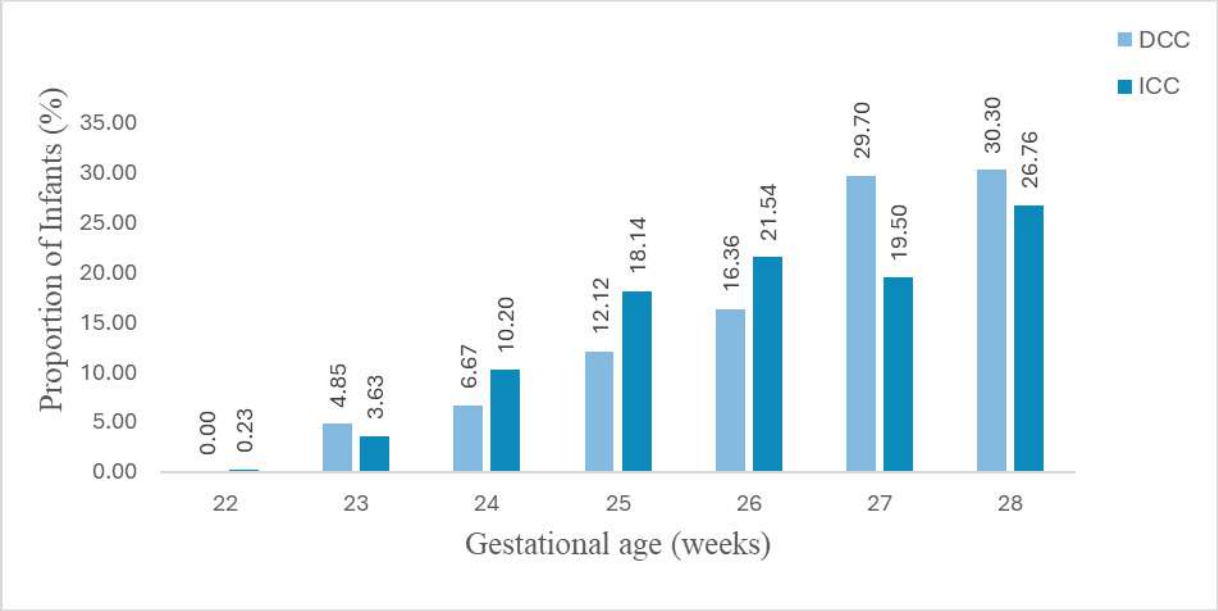

Figure 5. Bar diagram showing comparison of gestational age (weeks) in DCC & ICC groups.

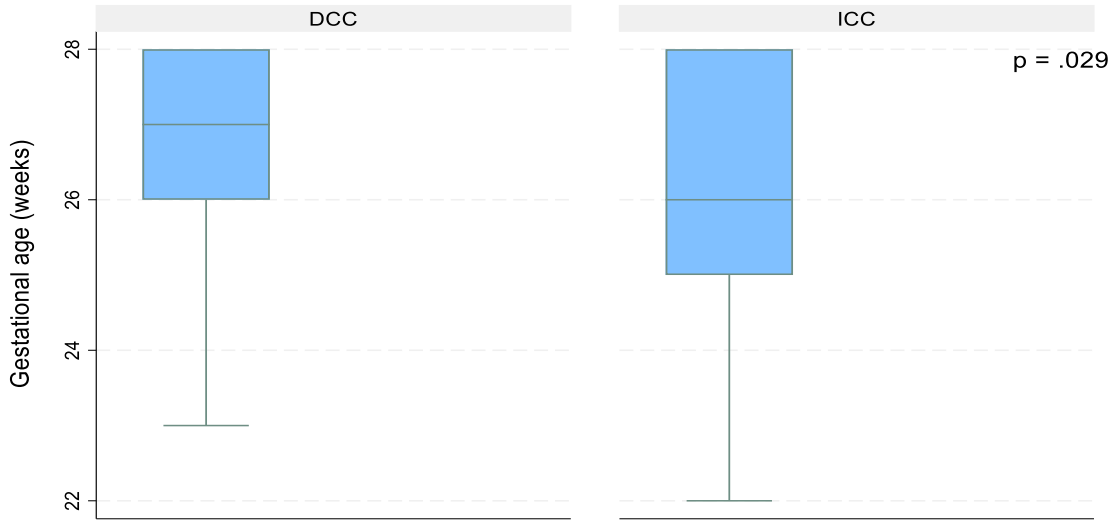

Figure 6. Box Plot showing distribution of gestational age in the DCC & ICC groups.

In general, the number of preterm infants in both groups increased with higher gestational ages, except for a slight decrease at 27 weeks in the ICC category (**Figure 5**). According to the box plot, the distribution of GA was skewed in both groups, primarily due to the smaller number of infants in the lower gestational age categories. The median gestational age in the DCC group was 27 (IQR: 26–28) weeks, while in the ICC group it was 26 (25–28) weeks (**Figure 6**). A statistically significant difference was observed in median gestational age between the two groups using the Mann–Whitney U test (p = .029).

Birth Weight

The data on birth weight were available for all 606 (100%) infants. The distribution of birth weight was slightly skewed among infants in the ICC group. The median birth weight in the DCC group was 870 (IQR: 750–1150) grams, while in the ICC group, it was 865 (750–1100)

grams. The Mann-Whitney U test indicated that median birth weight was similar between the two groups (p = .229); (**Figure 7**).

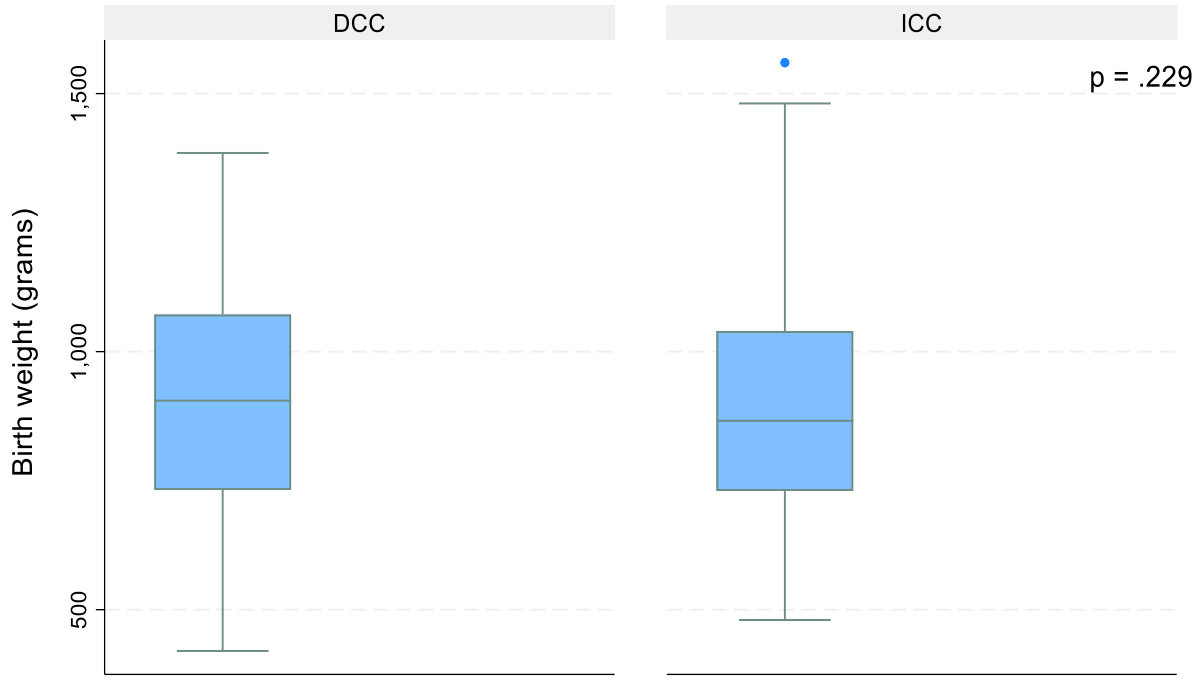

Figure 7. Box Plot showing distribution of birth weight in DCC & ICC group.

Sex of the Infants

Data on sex were available for 606 (100%)) infants. Sex was coded as 0 for female and 1 for male. The proportion of males was similar (55.15% vs 55.56%, p=.929); (**Table 16**).

Table 16. Comparison of neonatal sex in DCC & ICC Groups

Sex	**DCC Group (n = 165)**	**ICC Group (n = 441)**	**p-value***
Male. n (%)	91 (55.15)	245 (55.56)	.929
Female, n (%)	74 (44.85)	196 (44.44)	

*p-value obtained using Chi-squared test

Small for Gestational Age (SGA)

Data on small for gestational age (SGA), defined as birth weight below the 10th percentile, were available for all 606 (100%)) infants. A higher proportion of infants in the DCC group were classified as SGA compared to the ICC group (10.91% vs. 6.12%). This difference was statistically significant (p = .045); (**Table 17**).

Table 17. Comparison of SGA status in DCC & ICC Groups

Small for Gestational Age	**DCC Group (n = 165)**	**ICC Group (n = 441)**	**p-value***
Yes, n (%)	18 (10.91)	27 (6.12)	.045[a]
No, n (%)	147 (89.09)	414 (93.88)	

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

Apgar Scores at 5 minutes <7

The Apgar score is a measure of a newborn's well being at birth and indicates the effectiveness of resuscitation, if required. It is assessed at 1 and 5 minutes after birth. Data were available for 601 (99.17%)) infants. The distribution was skewed left in the DCC group, but symmetric with outliers in the ICC group; (**Figure 8**). The median (IQR) Apgar score at 5 minutes was 8 (6– 8) in the DCC group and 7 (6–8) in the ICC group, indicating a slightly higher score among infants who received DCC. Mann-Whitney U test showed statistically significant difference in the median of 5-minute Apgar score between the two groups (p = .023), although this difference was not considered clinically significant.

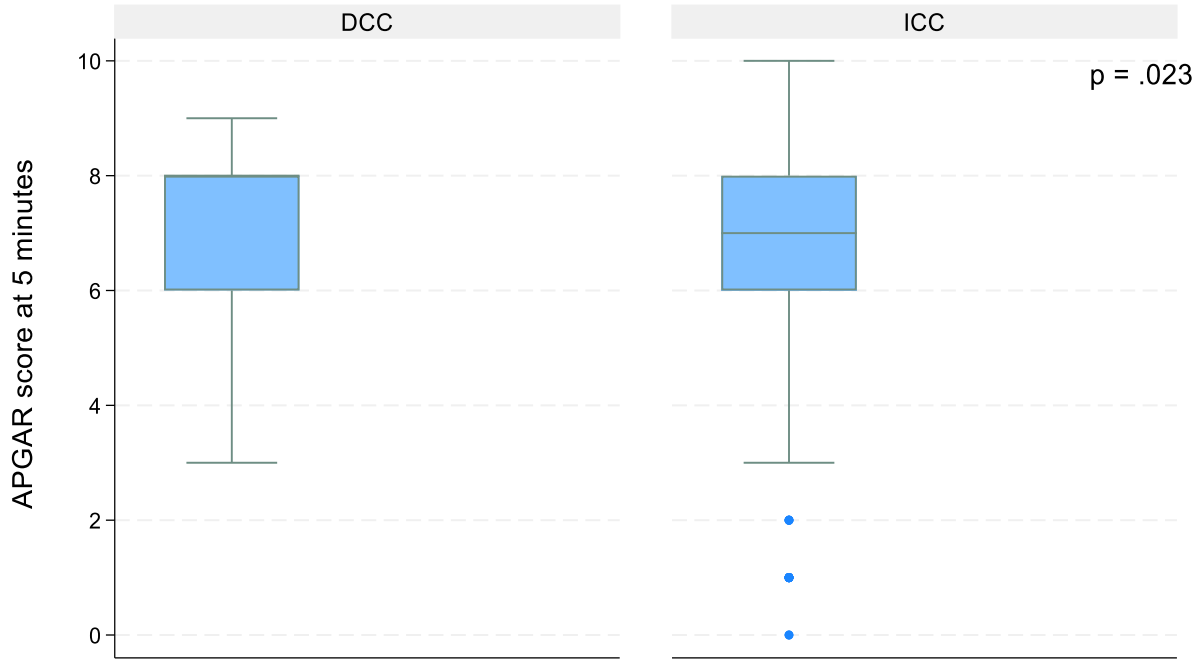

Figure 8. Box plots showing Apgar score at 5 minutes in DCC & ICC group.

The 5- minute Apgar score was categorized as 0 for Apgar score ≥7 and 1 for <7. The proportion of infants with scores <7 was similar between the DCC and ICC groups (29.70% vs 34.17%; p = .297); (**Table 18**).

Table 18. Comparison of Apgar score at 5 min <7 among infants in DCC & ICC Groups

Apgar score at 5 minutes <7	**DCC Group (n = 165)**	**ICC Group (n = 436)**	**p-value***
Yes, n (%)	49 (29.70)	149 (34.17)	.297
No, n (%)	116 (70.30)	287 (65.83)	

*p-value obtained using Chi-squared test

Baseline Characteristics of the Infants

The baseline demographic characteristics of preterm infants were illustrated in **Table 19**.

Table 19. Demographic characteristics in infants received DCC and ICC at birth

Demographic Characteristics	DCC Group (n = 165)	ICC Group (n = 441)	p-value*
GA- weeks, median (IQR)	27 (26–28)	26 (25–28)	.029[a]
Birth weight-grams, median (IQR)	870 (750–1150)	865 (750–1100)	.229
Male sex	91/165 (55.15)	245/441 (55.56)	.929
SGA	18/165 (10.91)	27/441 (6.12)	.045[a]
Apgar score at 5 minutes <7	49/165 (29.70)	149/436 (34.17)	.297

*Mann-Whitney U test for continuous variables which are not normally distributed and Chi-squared test for categorical variable
[a] Indicates statistical significance
Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise
The variables have different denominators because not all variables had all data available
DCC: deferred cord clamping; ICC: immediate cord clamping; GA: gestational age; SGA: small for gestational age (<10th percentile)

Preterm infants in the DCC group were delivered at a slightly higher gestational age and the proportion of SGA infants was significantly higher compared to the ICC group.

Neonatal Short-Term Outcomes

Maternal and infant baseline variables that showed significant associations with DCC—such as GA, ANCS, antibiotic use, smoking status, material deprivation quintiles, and SGA, were included in the analysis as confounding factors to adjust the estimates of short-term outcomes. Additionally, for the outcomes of retinopathy of prematurity (ROP) and severe ROP, the estimates were also adjusted for the duration of oxygen supplementation (166).

Respiratory Distress Syndrome (RDS)

Data on RDS were available for 605 (99.83%) infants. Proportion of infants who developed RDS was 90.30% in DCC and 94.09% in ICC group. The unadjusted odds ratio (OR) was 0.58 (95%

CI: 0.29–1.20); however, the association did not reach statistical significance (p = .103); (**Table 20**).

Table 20. Association between DCC and RDS (n = 605)

Exposure	RDS (yes) n (%)	RDS (no) n (%)	Total n (%)	Odds RDS (yes)/ RDS (no)	Odds Ratio (95% CI)	p-value*
DCC	149 (90.30)	16 (9.70)	165 (100)	9.31	0.58 (0.29–1.20)	.103
ICC	414 (94.09)	26 (5.91)	440 (100)	15.92		

*p-value obtained using Chi-squared test
RDS: respiratory distress syndrome

Notably, the association between DCC and RDS remained insignificant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (adjusted OR, AOR: 0.74, 95% CI 0.37–1.47, p = .389).

Bronchopulmonary Dysplasia (BPD)

Data on BPD were available for 556 (91.75%) infants. Although the proportion of BPD was lower in the DCC group compared to the ICC (53.13% vs 60.35%), the association was not statistically significant, unadjusted OR: 0.74 (95% CI: 0.51–1.10, p = .117); (**Table 21**).

Table 21. Association between DCC and BPD (n = 556)

Exposure	BPD (yes) n (%)	BPD (no) n (%)	Total n (%)	Odds BPD (yes)/ BPD (no)	Odds Ratio (95% CI)	p-value*
DCC	85 (53.13)	75 (46.87)	160 (100)	1.13	0.74 (0.51–1.10)	.117
ICC	239 (60.35)	157 (39.65)	396 (100)	1.52		

*p-value obtained using Chi-squared test
BPD: bronchopulmonary dysplasia

Notably, the association between DCC and BPD also remained insignificant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.84, 95% CI: 0.56–1.27, p = .418).

Patent Ductus Arteriosus (PDA)

Data on PDA were available for 602 (99.34%) infants. The proportion of PDA was lower in infants who received DCC compared to those who received ICC (57.58% vs 67.28%) and this association was statistically significant, OR: 0.66 (95% CI: 0.45 – 0.97), p = .026); (**Table 22**).

Table 22. Association between DCC and PDA (n = 602)

Exposure	PDA (yes) n (%)	PDA (no) n (%)	Total n (%)	Odds PDA (yes)/ PDA (no)	Odds Ratio (95% CI)	p-value*
DCC	95 (57.58)	70 (42.42)	165 (100)	1.36	0.66 (0.45–0.97)	.026[a]
ICC	294 (67.28)	143 (32.72)	437 (100)	2.06		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
PDA: patent ductus arteriosus

However, after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles, the association between DCC and PDA was no longer significant (AOR: 0.87, 95% CI: 0.58–1.32, p= .525).

Surgical Ligation

Among infants with PDA, 14 (8.48%) in the DCC group underwent surgical ligation, compared to 91 (20.82%) in the ICC group. The unadjusted OR was 0.35 (95% CI: 0.18–0.65) and this association was statistically significant (p = .001, **Table 23**).

Table 23. Association between DCC and PDA treated with surgical ligation (n = 602)

Exposure	Ligation (yes) n (%)	Ligation (no) n (%)	Total n (%)	Odds Ligation (yes)/ Ligation (no)	Odds Ratio (95% CI)	p-value*
DCC	14 (8.48)	151 (91.52)	165 (100)	0.09	0.35 (0.18–0.65)	.001[a]
ICC	91 (20.82)	346 (79.18)	437 (100)	0.26		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
PDA: patent ductus arteriosus

Of note, the association between DCC and surgically treated PDA remained statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.44, 95% CI: 0.23–0.85, p= .015).

Neonatal Sepsis

Data on neonatal sepsis were available for 604 (99.67%) infants. There was a statistically significant difference in the proportion of sepsis between DCC and ICC groups (11.52% vs 24.83%; p = < .001). The unadjusted OR was 0.39 (95% CI: 0.22–0.68) and these association reached statistical significance (p = .001, **Table 24**).

Table 24. Association between DCC and Neonatal Sepsis (n = 604)

Exposure	Sepsis (yes) n (%)	Sepsis (no) n (%)	Total n (%)	Odds Sepsis (yes)/ Sepsis (no)	Odds Ratio (95% CI)	p-value*
DCC	19 (11.52)	146 (88.48)	165 (100)	0.13	0.39 (0.22–0.68)	.001[a]
ICC	109 (24.83)	330 (75.17)	439 (100)	0.33		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

Of interest, the association between DCC and neonatal sepsis remained statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.42, 95% CI: 0.24–0.73; p= .002).

Intraventricular Haemorrhage (IVH)

Data on IVH were available for 604 (99.67%) infants. The proportion of infants who had IVH was 29.70% in the DCC and 30.75% in the ICC group. The unadjusted OR was 0.95 (95% CI: 0.63 – 1.43), p = .802; (**Table 25**).

Table 25. Association between DCC and IVH (n = 604)

Exposure	IVH (yes) n (%)	IVH (no) n (%)	Total n (%)	Odds IVH (yes)/ IVH (no)	Odd Ratio (95% CI)	p-value*
DCC	49 (29.70)	116 (70.30)	165 (100)	0.42	0.95 (0.63–1.43)	.802
ICC	135 (30.75)	304 (69.25)	439 (100)	0.44		

*p-value obtained using Chi-squared test
IVH: intraventricular haemorrhage

The association between DCC and IVH also remained insignificant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 1.34, 95% CI: 0.86–2.09, p = .188).

Severe IVH

The proportion of severe IVH (grade 3 or grade 4 IVH) was similar in both groups (15.15% vs 12.30%). The unadjusted OR was 1.27 (95% CI: 0.73–2.17), p = .354; (**Table 26**).

Table 26. Association between DCC and severe IVH (grade 3 or 4) (n = 604)

Exposure	s-IVH (yes) n (%)	s-IVH (no) n (%)	Total n (%)	Odds s-IVH (yes)/ s-IVH (no)	Odd Ratio (95% CI)	p-value*

DCC	25 (15.15)	140 (84.85)	165 (100)	0.18	1.27 (0.73–2.17)	.354
ICC	54 (12.30)	385 (87.70)	439 (100)	0.14		

*p-value obtained using Chi-squared test
s-IVH: severe intraventricular haemorrhage

Of interest, the association between DCC and severe IVH became statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 1.97, 95% CI: 1.09–3.55, p = .025).

Periventricular Leukomalacia (PVL)

Data on PVL were available for 603 (99.50%) infants. The proportion of infants who had PVL was similar in the DCC and ICC groups (2.42% vs 3.65%) and the association was not statistically significant 0.65 (95% CI: 0.16–2.07), p = .452; (**Table 27**).

Table 27. Association between DCC and PVL (n = 603)

Exposure	**PVL (yes) n (%)**	**PVL (no) n (%)**	**Total n (%)**	**Odds PVL (yes)/ PVL (no)**	**Odds Ratio (95% CI)**	**p-value***
DCC	4 (2.42)	161 (97.58)	165 (100)	0.02	0.65 (0.16–2.07)	.452
ICC	16 (3.65)	422 (96.35)	438 (100)	0.03		

*p-value obtained using Fisher's Exact test
PVL: periventricular leukomalacia

Of interest, the association between DCC and PVL was also not statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.77, 95% CI: 0.23–2.56, p = 0.671).

Severe Neurological Injury (SNI):

Data on SNI were available for 605 (99.82%) infants. The proportion was relatively high among the infants in the DCC group compared to the ICC group (15.15% vs 11.82), but the association was not statistically significant, unadjusted OR 1.33, (95% CI: 0.76–2.28), p = .273; **Table 28**).

Table 28. Association between DCC and Severe SNI (n = 605).

Exposure	SNI (yes) n (%)	SNI (no) n (%)	Total n (%)	Odds SNI (yes)/ SNI (no)	Odds Ratio (95% CI)	p-value*
DCC	25 (15.15)	140 (84.85)	165 (100)	0.17	1.33 (0.76–2.28)	.278
ICC	52 (11.85)	387 (88.15)	439 (100)	0.13		

*p-value obtained using Chi-squared test
SNI: severe neurologic injury

However, the association between DCC and SNI became statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 1.94, 95% CI: 1.08–3.46, p = .026).

Necrotising Enterocolitis (NEC)

NEC is categorized into several stages as per modified Bell's criteria and presence of stage II or higher was considered as positive outcome for this study. Data on NEC were available for 605 (99.83%) infants. The proportion of infants with confirmed NEC was lower in DCC compared to the ICC group (8.48% vs 11.59). The unadjusted OR was 0.71 (95% CI: 0.35–1.34) and the association was not statistically significant (p = .272; **Table 29**).

Table 29. Association between DCC and NEC (n = 605)

Exposure	NEC (yes) n (%)	NEC (no) n (%)	Total n (%)	Odds NEC (yes)/ NEC (no)	Odds Ratio (95% CI)	p-value*

DCC	14 (8.48)	151 (91.52)	165 (100)	0.09	0.71 (0.35–1.34)	.272
ICC	51 (11.59)	389 (88.41)	440 (100)	0.13		

*p-value obtained using Chi-squared test
NEC: necrotising enterocolitis

Of interest, the association between DCC and NEC was also not statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.76, 95% CI: 0.39–1.47, p= .419).

Retinopathy of Prematurity (ROP)

Data on ROP were available for 508 (83.83%) infants. The proportion of infants diagnosed with ROP (all stages) was comparable between the two groups (76.47% vs 74.65%) and the association was not significant 1.10 (95% CI: 0.69–1.77), p = .662; (**Table 30**).

Table 30. Association between DCC and ROP (n = 508)

Exposure	**ROP (yes) n (%)**	**ROP (no) n (%)**	**Total n (%)**	**Odds ROP (yes)/ ROP (no)**	**Odds Ratio (95% CI)**	**p-value***
DCC	117 (76.47)	36 (23.53)	153 (100)	3.25	1.10 (0.69–1.77)	.662
ICC	265 (74.65)	90 (25.35)	355 (100)	2.94		

*p-value obtained using Chi-squared test
ROP: retinopathy of prematurity

The association between DCC and ROP was also not statistically significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA, material deprivation quintiles and duration of oxygen as potential confounders (AOR 1.67, 95% CI: 0.96–2.92, p = .069).

Severe ROP

The proportion of severe ROP was significantly lower among DCC infants (7.19% vs 27.32%; p = < .001) compared to ICC. This association was statistically significant, 0.21 (95% CI: 0.10–0.40); p = < .001; (**Table 31**).

Table 31. Association between DCC and Severe ROP (n = 508)

Exposure	Severe ROP (yes) n (%)	Severe ROP (no) n (%)	Total n (%)	Odds sROP (yes)/ sROP (no)	Odds Ratio (95% CI)	p-value*
DCC	11 (7.19)	142 (92.81)	153 (100)	0.08	0.21 (0.10–0.40)	< .001[a]
ICC	97 (27.32)	258 (72.68)	355 (100)	0.38		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
ROP: retinopathy of prematurity

The association between DCC and severe ROP was continued to be significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA, material deprivation quintiles and duration of oxygen as potential confounders (AOR: 0.21, 95% CI: 0.10–0.46, p = < .001).

Discharge Home on Oxygen

Data on discharge home with oxygen were available for 596 (98.35%) infants. The proportion of infants discharged with oxygen was lower in the DCC groups compared to the ICC group (52.76% vs 74.60%). The unadjusted OR was 0.38 (95% CI: 0.26–0.56) and was statistically significant (p = <.001); (**Table 32**).

Table 32. Association between DCC and discharge home on oxygen (n = 596)

Exposure	Discharge home on Oxygen (yes) n (%)	Discharge home on Oxygen (no) n (%)	Total n (%)	Odds (yes)/ (no)	Odds Ratio (95% CI)	p-value*
DCC	86 (52.76)	77 (47.24)	163 (100)	1.11	0.38 (0.26–0.56)	< .001[a]

ICC	323 (74.60)	110 (25.40)	433 (100)	2.94

*p-value obtained using Chi-squared test
[a] Indicates statistical significance

The association between DCC and discharge home on oxygen remained significant after adjusting for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles as potential confounders (AOR: 0.35, 95% CI: 0.23–0.53, p = < .001).

Number of RBC / Whole Blood Transfusion

Data were available for 596 (98.35%)) infants. The distribution of number of required transfusions in DCC and ICC groups is shown in **Figure 9**. Mann-Whitney U test was used due to skewed distribution of the data, presence of outliers and the difference in standard deviation (SD) between groups. The median (IQR) number of RBC/whole blood transfusion was lower in the infants who received DCC, 0 (0–2) transfusions compared to those who received ICC, 3 (0–4) transfusions. This difference was statistically significant (p = < .001).

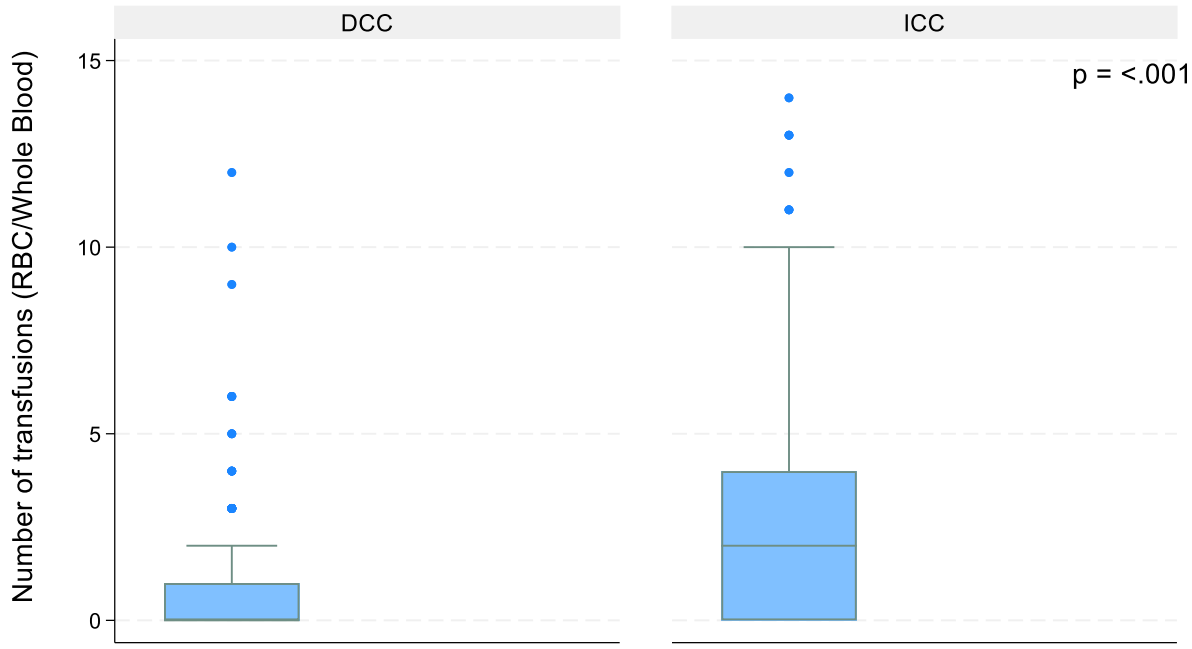

Figure 9. Box plots of number of blood transfusion received by DCC and ICC infants.

Duration of Mechanical Ventilation

Mechanical ventilation provides respiratory support for the premature infants via endotracheal tube (conventional positive pressure ventilator or high frequency ventilation). Data were available for 354 (58.42%) infants. The distribution across both groups is shown in **Figure 10**. Mann–Whitney U test was performed. The median (IQR) duration of mechanical ventilation was shorter in DCC infants, 2 (1–11) days compared to ICC infants, 3 (1–16) days; however, the difference was not significant (p = .621).

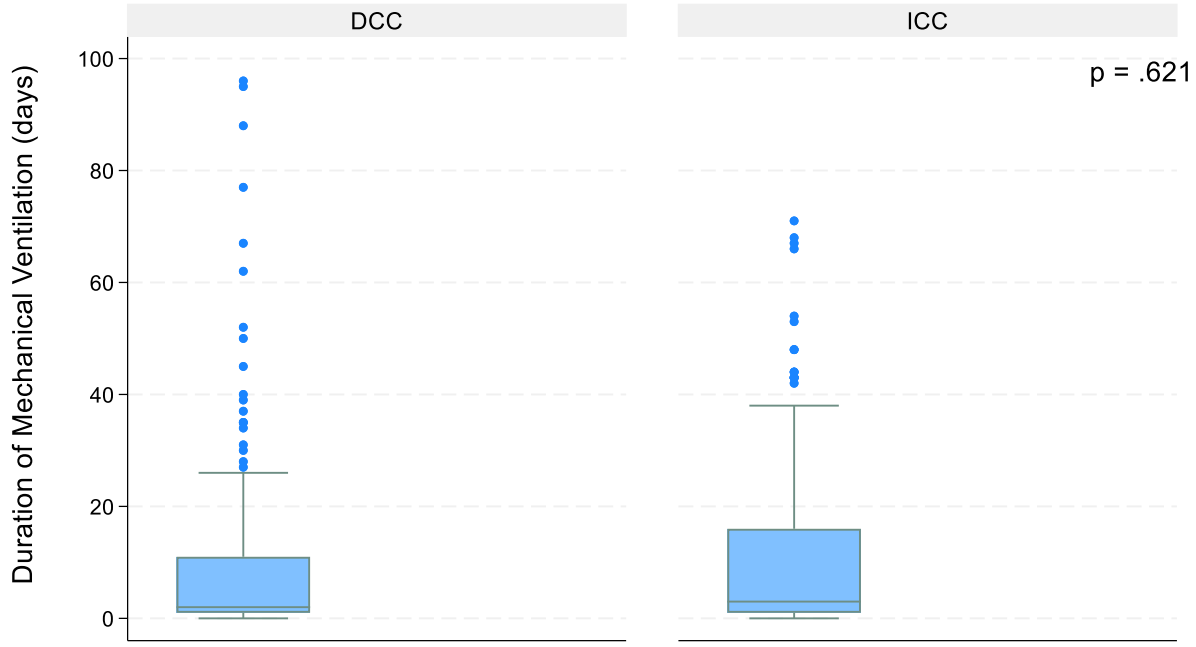

Figure 10. Box plots of duration of mechanical ventilation in infants received DCC and ICC.

Duration of non-invasive respiratory support

Non-invasive respiratory assists premature infants in breathing via CPAP (continuous positive airway pressure) or SiPAP (synchronized inspiratory positive airway pressure) or HFNC (high flow nasal canula/prongs) ≥ 1.5 LPM (litre per minute) or LFNC (low flow nasal canula/prongs) ≤ 1.5 LPM (litre per minute) with or without oxygen at 22%. The data were available for 331 (54.62%) infants. The distribution was slightly skewed with few outliers. The median (IQR) duration of non-invasive respiratory support was longer in DCC infants, 52 (40–60) days compared to ICC infants, 24 (10–45) days, (**Figure 11**). Mann–Whitney U test indicated a statistically significant difference between the two groups (p = < .001).

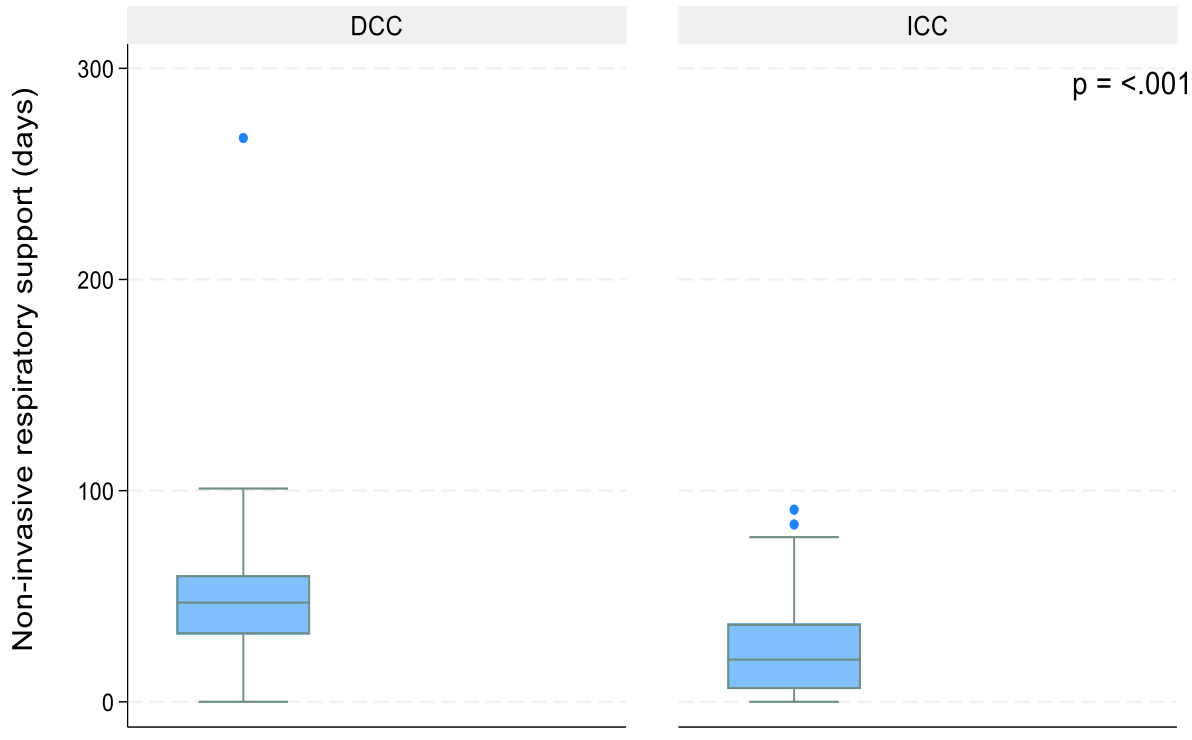

Figure 11. Box plots of duration of non-invasive respiratory support between DCC and ICC groups.

Duration of Oxygen Support

The data on the duration of oxygen support were available for 529 (87.29%) infants. The distribution was mildly skewed in the ICC group with outliers present in both groups. The median (IQR) duration of oxygen requirement was shorter in DCC infants, 150 (100–200) days compared to ICC infants, 200 (100–300) days and was statistically significant (p = .003); (**Figure 12**).

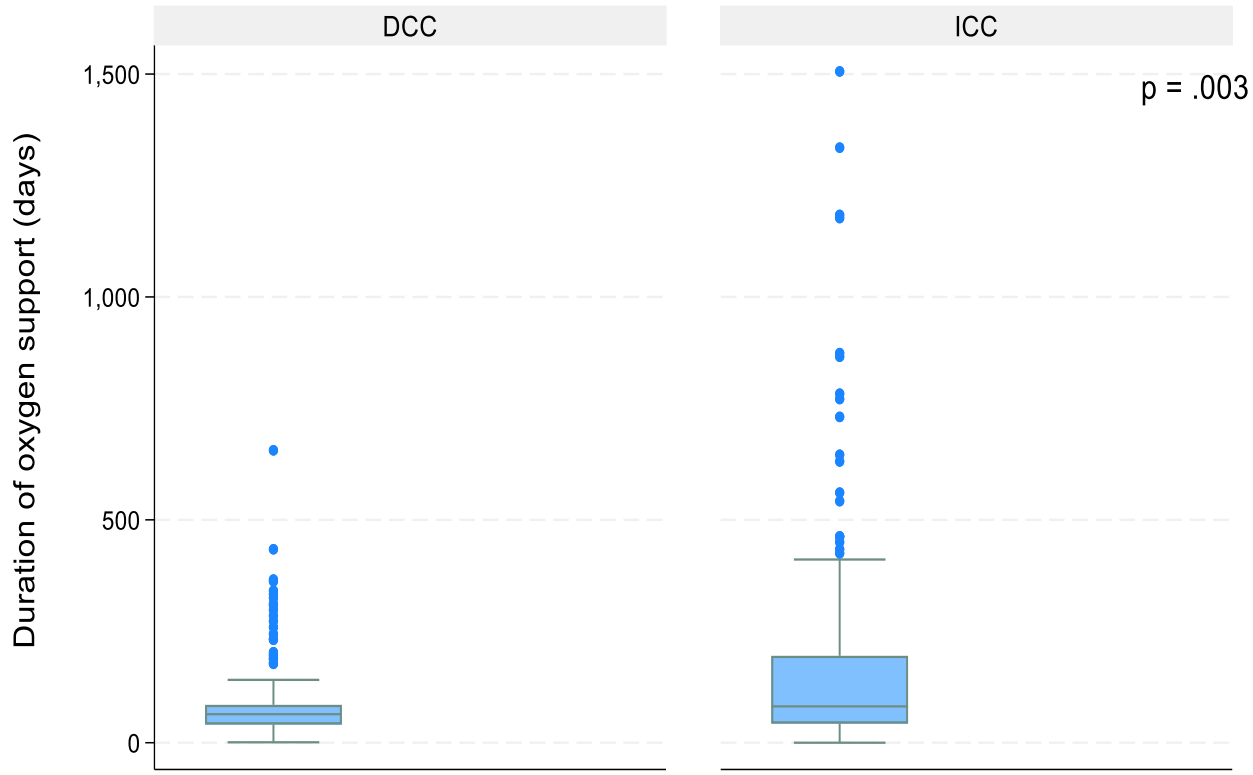

Figure 12. Box plots of duration of oxygen support in DCC and ICC infants.

Length of Stay at NICU

Data on the duration of NICU stay were available for 597 (98.51%) infants. The distribution was symmetric with a few outliers in both the DCC and ICC groups. The median length of NICU stay was 90 days (IQR: 80–110) in the DCC group and 89 days (IQR: 78–110) in the ICC group, (**Figure 13**). Mann-Whitney U test revealed a statistically significant difference in the length of NICU stay between the two groups (p = .032).

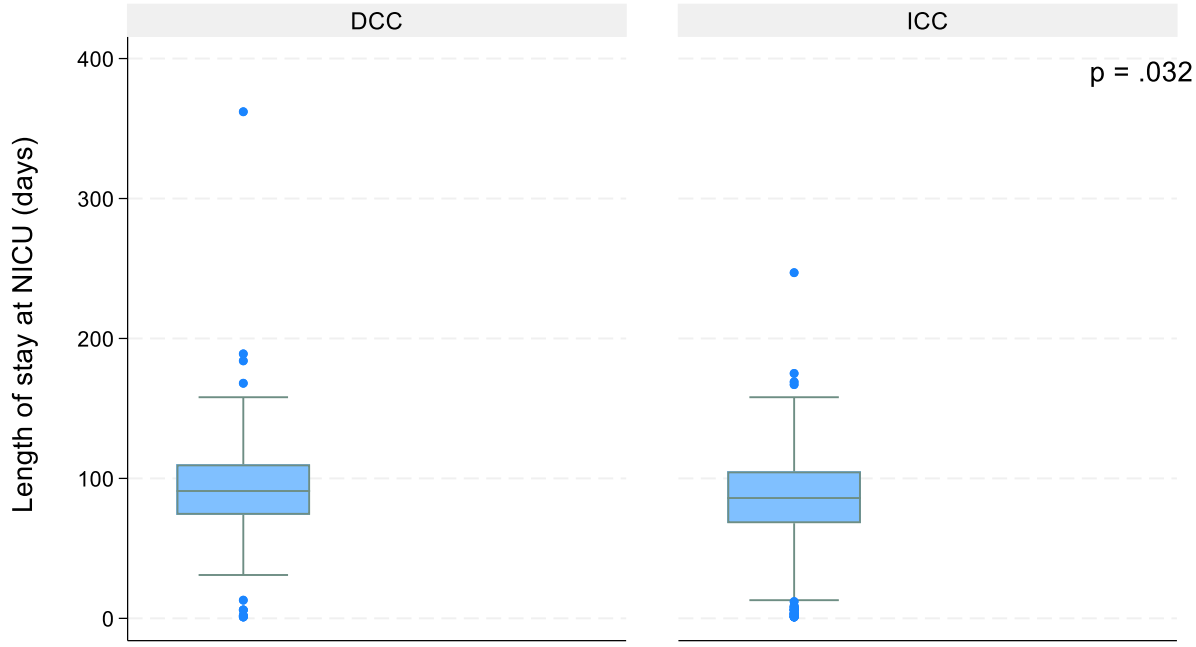

Figure 13. Length of stay (days) at NICU in DCC and ICC infants.

Short-term Neonatal Outcomes

Short-term neonatal outcomes are shown in **Table 33**.

Table 33. Short-term neonatal outcomes between DCC and ICC groups.

Neonatal Short-term Outcome	DCC Group (n = 165)	ICC Group (n =441)	Adjusted OR* (95% CI)	p-value
RDS	149/165 (90.30)	414/440 (94.09)	0.74 (0.37–1.47)	.389
BPD	85/160 (53.13)	239/396 (60.35)	0.84 (0.56–1.27)	.418
PDA	95/165 (57.58)	294/437 (67.28)	0.87 (0.58–1.32)	.525
Surg. treated PDA	14/165 (8.48)	91/437 (20.82)	0.44 (0.23–0.85)	.015[a]
Neonatal sepsis	19/165 (11.52)	109/439 (24.83)	0.42 (0.24–0.73)	.002[a]
IVH	49/165 (29.70)	135/439 (30.75)	1.34 (0.86–2.09)	.188
Severe IVH	25/165 (15.15)	54/439 (12.30)	1.97 (1.09–3.55)	.025[a]
PVL	4/165 (2.42)	16/438 (3.65)	0.77 (0.23–2.56)	.671
SNI	25/165 (15.15)	52/439 (11.85)	1.94 (1.08–3.46)	.026[a]
NEC, stage ≥ II	14/165 (8.48)	51/440 (11.59)	0.76 (0.39–1.47)	.419
ROP	117/153 (76.47)	265/355 (74.65)	1.67 (0.96–2.92)[£]	.069
Severe ROP	11/153 (7.19)	97/355 (27.32)	0.21 (0.10–0.46)[£]	< .001[a]
Discharge home on oxygen	86/163 (52.76)	323/433 (74.60)	0.35 (0.23–0.53)	< .001[a]

Number of transfusions, median (IQR)	0 (0–2)	3 (0–4)	N/A	< .001[a]
Total ventilation-days, median (IQR)	2 (1–11)	3 (1–16)	N/A	.621
Total non-invasive resp. support-days, median (IQR)	52 (40–60)	24 (10–45)	N/A	< .001[a]
Total suppl. Oxygen- days, median (IQR)	150 (100–200)	200 (100–300)	N/A	.003[a]
NICU Stay- days, median (IQR)	90 (80–110)	89 (78–110)	N/A	.032[a]

* Adjusted for GA, ANCS, antibiotics, smoking status, SGA and material deprivation quintiles
£ ROP and severe ROP also adjusted for duration of oxygen support
[a] Indicates statistical significance
Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise
The variables have different denominators because not all variables had all data available
BPD: bronchopulmonary dysplasia; DCC: deferred cord clamping; ICC: immediate cord clamping; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SNI: severe neurological injury
OR: odds ratio
N/A: not applicable

Bivariate analysis revealed that DCC in preterm infants was significantly associated with lower rates of PDA ligation, neonatal sepsis, severe ROP, frequency of blood transfusion, oxygen dependency at discharge home and fewer days of oxygen support during their NICU stay. However, the incidence of severe IVH and SNI was significantly higher, and the duration of non-invasive respiratory support and NICU stay was longer among them.

Mortality, Long-Term Neurodevelopmental Outcomes and Growth

Outcomes at 18-24 Months

Maternal and Neonatal Baseline Characteristics

The table below, (**Table 34**) presents the comparison of maternal and neonatal baseline characteristics of the preterm infants who received DCC or ICC and were evaluated at 18-24 months.

Table 34. Maternal and neonatal baseline characteristics of infants received DCC and ICC at 18-24 months corrected age (N= 567)

Maternal and Neonatal Characteristics	DCC Group (n = 153)	ICC Group (n = 414)	p-value*
Mothers' age in years, median (IQR)	33 (27–37)	30 (25–34)	< .001[a]
Completed high school	107/123 (86.99)	317/368 (86.14)	.812
PIH	31/153 (20.26)	56/308 (18.18)	.591
Gestational Diabetes	13/153 (8.50)	16/308 (5.19)	.169
Chorioamnionitis	34/153 (22.22)	100/392 (25.51)	.423
C-section	81/153 (52.94)	243/414 (58.70)	.219
ANCS	144/153 (94.12)	350/412 (84.95)	.003[a]
Maternal Antibiotics	108/153 (70.59)	248/409 (60.64)	.029[a]
Multiparous	73/153 (47.71)	179/399 (44.86)	.547
Multiple Birth	43/153 (28.10)	132/414 (31.88)	.387
PROM	46/153 (30.07)	108/410 (26.34)	.378
Smoking	14/153 (9.15)	94/411 (22.87)	< .001[a]
Alcohol use	8/153 (5.23)	21/410 (5.12)	.959
Material Deprivation Quintiles			
Quintile1 (most privileged)	24/146 (16.44)	57/371 (15.36)	.107
Quintile 2	30/146 (20.55)	67/371 (18.06)	
Quintile 3	29/146 (19.86)	67/371 (18.06)	
Quintile 4	16/146 (10.96)	79/371 (21.30)	
Quintile 5 (most deprived)	47/146 (32.19)	101/371 (27.22)	
Social Deprivation Quintiles			
Quintile1(most privileged)	24/146 (16.44)	60/371 (16.17)	.195
Quintile2	34/146 (23.29)	59/371 (15.90)	
Quintile3	29/146 (19.86)	69/371 (18.60)	
Quintile4	34/146 (23.29)	91/371 (24.53)	
Quintile5 (most deprived)	25/146 (17.12)	92/371 (24.80)	
GA in weeks, median (IQR)	27 (26–28)	26 (25–28)	.034[a]
Birth weight in grams, median (IQR)	850 (700–1100)	800 (710–1050)	.208
Male sex	84/153 (54.90)	224/414 (54.11)	.866
SGA	17/153 (11.11)	27/414 (6.52)	.070
Apgar score at 5 minutes <7	45/153 (29.41)	140/409 (34.23)	.279

*Mann-Whitney test for continuous variables and Chi-squared test for categorical variables.

[a] Indicates statistical significance

Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise

The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroids; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping; PIH: pregnancy induced hypertension PROM: prolonged rupture of the membrane; SGA: small for gestational age (<10th percentile)

Mothers in the DCC group were older, more likely to have received ANCS and antibiotics, but smoked less. Additionally, preterm infants in the DCC group were born at a slightly higher gestational age than those in the ICC group.

Assessment of Lost to follow-up children at 18 - 24 months

To account for attrition, a comparative analysis was carried out between children assessed at 18–24 months CA and those who were lost to follow-up. The analysis focused on baseline maternal and neonatal characteristics as well as short-term neonatal morbidities and was performed separately for the DCC and ICC groups, as shown in **Table 35**. The goal was to gain a thorough understanding of any potential differences between the followed-up and lost to follow-up cohorts. A total 39 children were lost to follow-up,12 from DCC group and 27 from ICC group. There was no significant difference in the proportion of children lost to follow-up between groups (7.27% vs 6.12%, p= .612).

Table 35. Comparison between Evaluated and Lost to Follow-Up in DCC and ICC Group

	DCC (N= 165)		**ICC (N= 441)**	
Demographic Characteristics and short-term outcomes	**Evaluated (n= 153)**	**Lost Follow-up (n = 12)**	**Evaluated (n= 414)**	**Lost Follow-up (n= 27)**
Maternal age in years, median (IQR)	33[a] (28–37)	27 (22–35)	30 (25–33)	28 (22–32)
Completed high school	107/123 (86.99)	5/5 (100)	317/368 (86.14)	7/10 (70)
PIH	32/153 (20.91)	1/12 (8.33)	56/308 (18.18)	2/22 (9.09)
Gestational diabetes	13/153 (8.50)	1/12 (8.33)	16/308 (5.19)	2/22 (9.09)
Chorioamnionitis	34/153 (22.22)	2/12 (16.67)	100/392 (25.51)	5/26 (19.23)
C-section	81/153 (52.94)	6/12 (50)	243/414 (58.70)	15/27 (55.56)
ANCS	144/153 (94.12)	11/12 (91.67)	350/412 (84.95)	23/25 (92)

Maternal antibiotics	107/153 (69.93)	9/12 (75)	247/409 (60.39)	18/25 (72)
Multiparous	73/153 (47.71)	8/12 (66.67)	179/399 (44.86)	12/26 (46.15)
Multiple Birth	42/153 (27.45)	3/12 (25)	132/414 (31.88)	11/27 (40.74)
PROM	46/153 (30.06)	3/12 (25)	108/410 (26.34)	5/26 (19.23)
Smoking	14/153 (9.15)	2/12 (16.67)	94/411[a] (22.87)	11/27 (40.74)
Alcohol use	8/153 (5.23)	0/12 (0)	21/410 (5.12)	1/27 (3.70)
Material deprivation Quintiles				
Quintile1 (most privileged)	24/146 (16.44)	3/12 (25)	57/372 (15.32)	4/25 (16)
Quintile2	31/146 (21.23)	2/12 (16.67)	67/372 (18.01)	3/25 (12)
Quintile3	29/146 (19.86)	1/12 (8.33)	67/372 (18.01)	3/25 (12)
Quintile4	15/146 (10.27)	2/12 (16.67)	80/372 (21.51)	9/25 (36)
Quintile5 (most deprived)	47/146 (32.20)	4/12 (33.33)	101/372 (27.15)	6/25 (24)
Social deprivation Quintiles				
Quintile1 (most privileged)	24/146 (16.44)	3/12 (25)	60/372 (16.13)	3/25 (12)
Quintile2	33/146 (22.60)	1/12 (8.33)	59/372 (15.86)	2/25 (8)
Quintile3	29/146 (19.86)	3/12 (25)	69/372 (18.55)	6/25 (24)
Quintile4	34/146 (23.29)	2/12 (16.67)	91/372 (24.46)	6/25 (24)
Quintile5 (most deprived)	26/146 (17.81)	3/12 (25)	93/372 (25)	8/25 (32)
GA in weeks, median (IQR)	27 (26–28)	27.5 (25–28)	26 (25–28)	26 (26–28)
Birth weight in gram, median (IQR)	900 (750–1100)	950 (800–1170)	850[a] (700–1150)	950 (850–1300)
Male	84/153 (54.90)	7/12 (58.33)	224/414[a] (54.11)	21/27 (77.78)
SGA	17/153 (11.11)	1/12 (8.33)	27/414 (6.52)	0/27 (0)
Apgar at 5 minutes <7	45/153 (29.41)	4/12 (33.33)	139/409 (33.98)	10/27 (37.04)

RDS	138/153 (90.20)	11/12 (91.67)	390/413 (94.43)	24/27 (88.89)
BPD	80/153 (53.69)	5/12 (45.45)	226/375 (60.27)	13/21 (61.90)
PDA	89/153 (58.17)	6/12 (50)	277/412 (67.23)	17/25 (68)
Surg. treated PDA	13/153 (8.50)	1/12 (8.33)	86/412 (20.87)	5/25 (20)
Sepsis	17/153 (11.11)	2/12 (16.67)	106/413 (25.66)	3/26 (11.54)
IVH	47/153 (30.72)	2/12 (16.67)	127/413 (30.75)	8/26 (30.77)
Severe IVH	24/153 (15.69)	1/12 (8.33)	50/413 (12.11)	4/26 (15.38)
PVL	4/153 (2.61)	0/12 (0)	16/412 (3.88)	0/26 (0)
SNI	24/153 (15.69)	1/12 (8.33)	48/413 (11.62)	4/27 (14.81)
NEC, stage ≥ II	12/153 (7.84)	2/12 (16.67)	48/414 (11.59)	3/26 (11.54)
ROP	108/142 (76.05)	9/11 (81.82)	259/344 (75.29)	6/10 (60)
Severe ROP	11/142 (7.75)	0/11 (0)	96/344 (27.83)	1/10 (10)
Discharge home on oxygen	77/151 (50.99)	9/12 (75)	303/408 (74.26)	20/25 (80)
Number of transfusions median (IQR)	0 (0–2)	1 (0–3)	2 (0–4)	1.5 (0–3)
Total ventilation-days, median (IQR)	1 (0–10)	1 (0–15)	2.5 (1.5–16)	2 (0–10)
Non-invasive resp. support Days, median (IQR)	60 (40–70)	58 (42–68)	20 (8–40)	18 (4–24)
Total suppl. oxygen-days median (IQR)	75 (50–100)	50 (45–120)	100 (50–250)	75 (50–200)
NICU stay-days, median (IQR)	95 (87–110)	90 (85–115)	80[a] (60–110)	75 (50–100)

* Mann-Whitney U test for continuous variables which are not normally distributed, Chi-squared test for categorical variables and Fisher's exact test when the cell count <5

[a] Indicates statistical significance

Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR) unless specified otherwise

The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroids, BPD: bronchopulmonary dysplasia; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the membrane; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SGA: small for gestational age (<10th percentile); SNI: severe neurological injury

In the DCC cohort, mothers who completed follow-up were significantly older than those who were lost to follow-up. In contrast, within the ICC cohort, mothers in the follow-up group had a lower prevalence of smoking during pregnancy and their infants had lower birth weights and a lower proportion of males. Additionally, infants in the follow-up group had significantly longer NICU stays compared to those lost to follow-up.

Definition of Neurodevelopmental Impairments

The primary outcome of our study was composite of death or any neurodevelopmental impairment (NDI).

Definition of NDI includes presence of any of the following outcomes: cerebral palsy (CP), Gross Motor Function Classification System (GMFCS) score ≥1; cognitive, motor or language delay, Bayley Scales of Infant Development, 3rd edition (BSID-III) scores of <85 on any component (at 18-24 months) or full scale IQ (FSIQ) <85 on the Wechsler Preschool and Primary Scale of Intelligence, 3rd or 4th edition (WPPSI-III or IV) at 36 months or >1SD below the mean; sensorineural hearing loss or auditory neuropathy with or without aid; visual impairment with corrected visual acuity of >20/60 in the better eye, or unilateral/bilateral blindness (156). The Leiter-R (Leiter international performance scale-revised) test is a non-verbal intelligence test suitable for non-English-speaking children. It has a mean of 100 and standard deviation of 15, consistent with WPPSI (157). Cognitive scores from the Leiter-R were categorized using the same classification scheme applied in the WPPSI assessment.

Definition of severe NDI (sNDI) includes presence of any of the following outcomes: cerebral palsy, GMFCS score ≥3; cognitive, motor or language delay, BSID-III scores of <70 on any component (at 18-24 months) or the WPPSI III or IV, scores of <70 (36 months) or >2SD below

the mean; bilateral sensorineural hearing loss or auditory neuropathy with aid; bilateral blindness (corrected visual acuity <20/200 in better eye) (122).

The outcome variable was coded as 0 if neither death nor NDI occurred and as 1 if either—death or any form of NDI—was identified at follow-up.

To ensure the accuracy and comparability, infants who died or showed signs of NDI without a confirmed diagnosis of cerebral palsy, cognitive delay, motor delay, language delay, hearing impairment, or visual impairment were excluded. This criterion ensured consistency in outcome definitions and to reduce the risk of misclassification.

Outcome – specific results

Death or any Neurodevelopmental Impairment (NDI)

Data on death or any NDI were available for 477 children, representing 78.71% of the total cohort (477 out of 606). Proportion of children with death or any NDI was 65.52% in DCC and 59.83% in ICC group. The unadjusted OR was 1.28 (95% CI: 0.81–2.03); however, the association did not attain statistical significance (p = .274); (**Table 36**).

Table 36. Association between DCC and Death or any NDI at 18-24 months (n = 477)

Exposure	Death/ NDI (yes), n (%)	Death/NDI (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	76 (65.52)	40 (34.48)	116 (100)	1.9	1.28 (0.81–2.03)	.274
ICC	216 (59.83)	145 (40.17)	361 (100)	1.49		

*p-value obtained using Chi-squared test
NDI: neurodevelopmental impairment

Death or severe Neurodevelopmental Impairments (sNDI)

The data on death or severe NDI were available for 439 children, representing 72.44% of the total cohort (439 out of 606). The proportion of death or severe NDI was lower in DCC group

compared to ICC group (25.96% vs 29.25%). The unadjusted OR was 0.85 (95% CI: 0.49–1.42); but the association was not statistically significant (p = .516); (**Table 37**).

Table 37. Association between DCC and death or severe NDI at 18-24 months (n = 439)

Exposure	Death/s-NDI (yes), n (%)	Death/ s-NDI (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	27 (25.96)	77 (74.04)	104 (100)	0.35	0.85 (0.49–1.42)	.516
ICC	98 (29.25)	237 (70.75)	335 (100)	0.41		

*p-value obtained using Chi-squared test
s-NDI: severe neurodevelopmental impairment

Any Neurodevelopmental Impairments (NDI)

Data on any NDI were available for 437 children, representing 72.11% of the total cohort (437 out of 606). The proportion of children with any NDI was relatively high in the DCC group compared to the ICC group (61.90% vs 56.33%). The unadjusted OR was 1.26 (95% CI: 0.79–2.03), but not statistically significant (p = .313); (**Table 38**).

Table 38. Association between DCC and any NDI at 18-24 months (n = 437)

Exposure	NDI (yes) n (%)	NDI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	65 (61.90)	40 (38.10)	105 (100)	1.62	1.26 (0.79–2.03)	.313
ICC	187 (56.33)	145 (43.67)	332 (100)	1.29		

*p-value obtained using Chi-squared test
NDI: neurodevelopmental impairment

Severe Neurodevelopmental Impairments (severe NDI)

Data on severe NDI were available for 399 children, representing 65.84% of the total cohort (399 out of 606). The proportion of children with severe NDI was lower in the DCC group compared to the ICC group (17.20% vs 22.55%). The unadjusted OR was 0.71 (95% CI: 0.36–1.33); however, the association was not statistically significant (p = .270); **Table 39**.

Table 39. Association between DCC and severe NDI at 18-24 months (n = 399)

Exposure	s-NDI (yes) n (%)	s-NDI (no) n (%)	Total n (%)	Odds (yes/ no)	Odds Ratio (95% CI)	p-value*
DCC	16 (17.20)	77 (82.80)	93 (100)	0.21	0.71 (0.36–1.33)	.270
ICC	69 (22.55)	237 (77.45)	306 (100)	0.29		

*p-value obtained using Chi-squared test
s-NDI: severe neurodevelopmental impairment

Cerebral Palsy (CP)

Cerebral palsy was considered present if a child had a GMFCS score ≥1. The data on CP were available for 313 surviving children, representing 51.65% of the total cohort (313 out of 606). The proportion of all grades CP was comparable between DCC and ICC groups (11.49% vs 14.60%). The unadjusted OR was 0.80 (95% CI: 0.32–1.68); indicating no statistically significant difference between groups (p = .474); (**Table 40**).

Table 40. Association between DCC and Cerebral palsy at 18-24 months (n = 313)

Exposure	CP (yes) n (%)	CP (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	10 (11.49)	77 (88.51)	87 (100)	0.13	0.80 (0.32–1.68)	.474
ICC	33 (14.60)	193 (85.40)	226 (100)	0.17		

*p-value obtained using Chi-squared test
CP: cerebral palsy

GMFCS scores were available for 35 of the 43 children diagnosed with cerebral palsy (81.40%). Severity was classified as mild (GMFCS 1), moderate (GMFCS 2 &3), and severe (GMFCS 4&5)(167). In the DCC group, 6 children (60%) had moderate CP, and 4 (40%) had mild CP. In the ICC group, 3 children (12%) had severe CP, 9 (36%) had moderate CP, and 13 (52%) had mild CP. The distribution of CP severity did not differ significantly between groups (p = .483), **Table 41**.

Table 41. Comparison of the severity of cerebral palsy between DCC and ICC groups (n=35)

Severity of CP	DCC Group (n = 10)	ICC Group (n = 25)	p-value*
Mild, n (%)	4 (40)	13 (52)	.483
Moderate, n (%)	6 (60)	9 (36)	
Severe, n (%)	0 (10)	3 (12)	

*p-value obtained using Chi-squared test
CP: cerebral palsy

Cognitive Delay

A delay in cognitive, motor, or language development was defined as a standardized score of <85 (>1SD below the mean) on the respective subscale of the BSID-III, assessed at 18 to 24 months corrected age(168). Data were available for 333 children, representing 54.95% of the total cohort (333 out of 606). The proportion of children delay in cognitive development was similar between two groups. (20.69% vs 29.27%, p= .121). The unadjusted OR was 0.63 (95% CI: 0.32–1.16) and the difference did not reach statistical significance, (**Table 42**).

Table 42. Association between DCC and Cognitive Delay at 18-24 months (n = 333)

Exposure	CD (yes) n (%)	CD (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	18 (20.69)	69 (79.31)	87 (100)	0.26	0.63 (0.32–1.16)	.121
ICC	72 (29.27)	174 (70.73)	246 (100)	0.41		

*p-value obtained using Chi-squared test
CD: cognitive delay

Motor Delay

Data on motor delay were available for 330 children, representing 54.46% of the total cohort (330 out of 606). The proportion for motor delay was 38.64% in the DCC group and 32.23% in

the ICC group. The unadjusted OR was 1.32 (95% CI: 0.77–2.26); however, the association was not statistically significant (p = .277); (**Table 43**).

Table 43. Association between DCC and Motor Delay at 18-24 months (n = 330)

Exposure	Motor Delay (yes), n (%)	Motor Delay (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	34 (38.64)	54 (61.36)	88 (100)	0.63	1.32 (0.77–2.26)	.277
ICC	78 (32.23)	164 (67.77)	242 (100)	0.48		

*p-value obtained using Chi-squared test

Language Delay

Data on language delay were available for 381 children, representing 62.87% of the total cohort (381 out of 606). The proportion were similar between the two groups, 47.78% in the DCC group vs. 45.70% in the ICC group. The unadjusted OR was 1.09 (95% CI: 0.66–1.79); however, the association was not statistically significant (p = .730); (**Table 44**).

Table 44. Association between DCC and Language Delay at 18-24 months (n = 381)

Exposure	Language Delay (yes), n (%)	Language Delay (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	43 (47.78)	47 (52.22)	90 (100)	0.91	1.09 (0.66–1.79)	.730
ICC	133 (45.70)	158 (54.30)	291 (100)	0.84		

*p-value obtained using Chi-squared test

Hearing Impairment

Hearing impairment in the study was defined as unilateral / bilateral sensorineural hearing loss or auditory neuropathy, whether or not amplification or cochlear implants were required. The data were available for 282 children, representing 46.53% of the total cohort (282 out of 606). The proportion was significantly different between groups (0% vs 7.80%, p = .012). Estimation of odds ratio was not possible due to the lack of observed outcomes in the DCC group, (**Table 45**).

Table 45. Association between DCC and Hearing Impairment at 18-24 months (n = 282)

Exposure	HI (yes) n (%)	HI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	0 (0)	77 (100)	77 (100)	0	N/A	.012[a]
ICC	16 (7.80)	189 (92.20)	205 (100)	0.08		

*p-value obtained using Fisher's Exact test
[a]Indicates statistical significance
HI: hearing impairment

Visual Impairment

Visual impairment in the study defined as corrected visual acuity of >20/60 in the better eye, or unilateral / bilateral blindness. The proportion of visual impairment was lower in the DCC group compared to the ICC group (1.28% vs 7.11%). The unadjusted odds ratio was 0.17 (95% CI: 0.01–1.14), however, the association was not statistically significant (p = .054); (**Table 46**).

Table 46. Association between DCC and Visual Impairment at 18-24 months (n = 289)

Exposure	VI (yes) n (%)	VI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	1 (1.28)	77 (98.72)	78 (100)	0.01	0.17 (0.01–1.14)	.054
ICC	15 (7.11)	196 (92.89)	211 (100)	0.08		

*p-value obtained using Fisher's Exact test
VI: visual impairment

Growth

Growth was assessed using the World Health Organization (WHO) growth standards(161). Weight (kg), height (cm), and head circumference (cm) measured at the 18-24-month follow-up were used to calculate z-scores to reflect a child's growth pattern. Poor growth was defined as any of these parameters falling below −2 z-scores according to WHO criteria (161, 169). To isolate the effect of DCC versus ICC exposure on small for gestational age (SGA) and

appropriate for gestational age (AGA) groups; the study cohort was stratified accordingly. Data were available for 35 children in the SGA and 449 children AGA cohort. For each subgroup, a two-sided independent t-tests were conducted to compare mean z-scores. None of the parameters fell below −2 z-scores and no statistically significant differences were observed; (**Table 47**).

Table 47. Comparison of Growth at 18-24 months

Growth Parameter	SGA-DCC (n=12)	SGA-ICC (n=23)	p-value	AGA-DCC (n= 121)	AGA-ICC (n=328)	p-value
Weight z-score, mean (SD)	-1.71 (1.17)	-1.51 (1.05)	.619	-0.44 (0.94)	-0.36 (1.13)	.484
Height z-score, mean (SD)	-1.31 (1.38)	-1.60 (1.21)	.520	-0.53 (1.01)	-0.56 (1.25)	.788
Head circumference z-score, mean (SD)	-0.77 (1.07)	-0.85 (1.11)	.853	0.22 (1.04)	-0.19 (1.27)	.833

*p-value obtained by two-sided t-test
DCC: deferred cord clamping; ICC: immediate cord clamping

Outcomes at 36 Months

Maternal and Neonatal Baseline Characteristics

The table below, (**Table 48**) presents the comparison of maternal and neonatal baseline characteristics of the preterm infants who received DCC or ICC and were evaluated at 36 months.

Table 48. Maternal and neonatal baseline characteristics of infants received DCC and ICC at 36 months corrected age (N= 521)

Maternal and Neonatal Characteristics	DCC Group (n = 145)	ICC Group (n = 376)	p-value*
Mothers' age in years, median (IQR)	33 (28–37)	30 (26–33)	< .001[a]
Completed high school	101/115 (87.83)	293/338 (86.69)	.754
PIH	30/145 (20.69)	46/279 (16.49)	.285

Gestational Diabetes	11/145 (7.59)	15/279 (5.38)	.368
Chorioamnionitis	29/145 (20)	92/355 (25.92)	.161
C-section	76/145 (52.41)	222/376 (59.04)	.171
ANCS	136/145 (93.79)	320/374 (85.56)	.010[a]
Maternal Antibiotics	101/145 (69.66)	232/371 (62.53)	.129
Multiparous	71/145 (48.97)	163/365 (44.66)	.378
Multiple Birth	39/145 (26.90)	126/376 (33.51)	.146
PROM	42/145 (28.97)	107/372 (28.76)	.964
Smoking	12/145 (8.28)	82/373 (21.98)	< .001[a]
Alcohol use	8/145 (5.52)	19/373 (5.09)	.846
Material Deprivation Quintiles			
Quintile1 (most privileged)	24/138 (17.39)	51/336 (15.18)	.194
Quintile 2	27/138 (19.57)	63/336 (18.75)	
Quintile 3	29/138 (21.01)	61/336 (18.15)	
Quintile 4	16/138 (11.59)	71/336 (21.13)	
Quintile 5 (most deprived)	42/138 (30.44)	90/336 (26.79)	
Social Deprivation Quintiles			
Quintile1(most privileged)	24/138 (17.39)	56/336 (16.67)	.258
Quintile2	31/138 (22.46)	54/336 (16.07)	
Quintile3	28/138 (20.30)	62/336 (18.45)	
Quintile4	31/138 (22.46)	78/336 (23.21)	
Quintile5 (most deprived)	24/138 (17.39)	86/336 (25.60)	
GA in weeks, median (IQR)	27 (26–38)	26 (25–28)	.049[a]
Birth weight in grams, median (IQR)	850 (700–1050)	800 (700–1020)	.201
Male sex	79/145 (54.48)	212/376 (56.38)	.695
SGA	16/145 (11.03)	27/376 (7.18)	.152
Apgar score at 5 minutes <7	44/145 (30.34)	125/371 (33.69)	.466

*Mann-Whitney test for continuous variables and Chi-squared test for categorical variables.
[a] Indicates statistical significance
Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise
The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroids; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the membrane; SGA: small for gestational age (<10th percentile)

Mothers in the DCC group were older, more likely to have received ANCS, and reported lower rates of smoking. Additionally, preterm infants in the DCC group were born at a slightly higher gestational age than those in the ICC group.

Assessment of Lost to follow-up Infants at 36 months

A total of 46 children were lost to follow-up by 36 months, including 8 from the DCC group and 38 from the ICC group. There was no statistically significant difference in the proportion of infants lost to follow-up between groups (5.23% vs. 9.18%, p = .273).

A comparative analysis of baseline maternal and neonatal characteristics, along with short-term neonatal morbidities, was conducted between children who completed follow-up and those lost to follow-up at 36 months corrected age. This analysis was performed separately for the DCC and ICC cohorts, (**Table 49**).

Table 49. Comparison between Evaluated and Lost to Follow-Up in DCC and ICC Cohort

	DCC (N= 153)		**ICC (N= 414)**	
Demographic Characteristics and Short-term outcomes	**Evaluated (n= 145)**	**Lost Follow-up (n = 8)**	**Evaluated (n= 376)**	**Lost Follow-up (n= 38)**
Maternal age in years, median (IQR)	33 (28–38)	28 (21–36)	30 (27–34)	27 (23–35)
Completed high school	103/117 (88.03)	4/6 (66.67)	293/338 (86.69)	24/30 (80)
PIH	31/145 (21.38)	1/8 (12.50)	46/279[a] (16.49)	10/29 (34.48)
Gestational diabetes	11/145 (7.58)	2/8 (25)	15/279 (5.38)	1/29 (3.45)
Chorioamnionitis	29/145[a] (20)	5/8 (62.5)	92/355 (25.91)	8/37 (21.62)
C-section	76/145 (52.41)	5/8 (62.5)	222/376 (59.04)	21/38 (55.26)

ANCS	136/145 (93.79)	8/8 (100)	320/374 (85.56)	30/38 (78.95)
Maternal antibiotics	100/145 (68.96)	7/8 (87.5)	232/371[a] (62.53)	15/38 (39.47)
Multiparous	71/145 (48.96)	2/8 (25)	163/365 (44.66)	16/34 (47.06)
Multiple Birth	38/145 (26.21)	4/8 (50)	126/376[a] (33.51)	6/38 (15.79)
PROM	41/145[a] (28.27)	5/8 (62.5)	105/372[a] (28.23)	3/38 (7.89)
Smoking	14/145 (9.65)	0/8 (0)	83/373 (22.25)	11/38 (28.95)
Alcohol use	8/145 (5.52)	0/8 (0)	18/373 (4.83)	3/37 (8.11)
Material deprivation Quintiles				
Quintile1 (most privileged)	24/138 (17.39)	0/8 (0)	52/338 (15.38)	5/34 (14.71)
Quintile2	28/138 (20.29)	3/8 (37.50)	63/338 (18.64)	4/34 (11.76)
Quintile3	29/138 (21.01)	0/8 (0)	61/338 (18.05)	6/34 (17.65)
Quintile4	15/138 (10.87)	0/8 (0)	72/338 (21.30)	8/34 (23.53)
Quintile5 (most deprived)	42/138 (30.44)	5/8 (62.50)	90/338 (26.63)	11/34 (32.35)
Social deprivation Quintiles				
Quintile1 (most privileged)	24/138 (17.30)	0/8 (0)	56/338 (16.57)	4/34 (11.76)
Quintile2	30/138 (21.74)	3/8 (37.50)	54/338 (15.98)	5/34 (14.71)
Quintile3	28/138 (20.29)	1/8 (12.50)	62/338 (18.34)	7/34 (20.59)
Quintile4	31/138 (22.46)	3/8 (37.50)	79/338 (23.37)	12/34 (35.29)
Quintile5 (most deprived)	25/138 (18.11)	1/8 (12.50)	87/338 (25.74)	6/34 (17.65)
GA, weeks, median (IQR)	27 (26–28)	27 (27–28)	26 (25–28)	26 (25–28)
Birth weight, grams, median (IQR)	900 (710–1050)	990 (790–1050)	850 (700–1200)	850 (700–1300)
Male	79/145 (54.48)	5/8 (62.5)	212/376[a] (56.38)	12/38 (31.58)
SGA	16/145	1/8	27/376	0/38

	(11.03)	(12.50)	(7.18)	(0)
Apgar at 5 minutes <7	44/145	1/8	125/371	14/38
	(30.34)	(12.50)	(33.69)	(36.84)
RDS	131/145	7/8	357/375[a]	33/38
	(90.34)	(87.50)	(95.20)	(86.84)
BPD	75/141	5/8	208/343	18/32
	(53.19)	(62.50)	(60.64)	(56.25)
PDA	82/145	7/8	252/374	25/38
	(56.55)	(87.50)	(66.84)	(65.79)
Surg. treated PDA	10/145[a]	3/8	80/374	6/38
	(6.90)	(37.5)	(21.39)	(15.79)
Sepsis	16/145	1/8	100/375	6/38
	(11.03)	(12.50)	(26.67)	(15.79)
IVH	46/145	1/8	118/375	9/38
	(31.72)	(12.50)	(31.47)	(23.68)
Severe IVH	24/145	0/8	48/375	2/38
	(16.55)	(0)	(12.80)	(5.26)
PVL	4/145	0/8	14/374	2/38
	(2.76)	(0)	(3.74)	(5.26)
SNI	24/145	0/8	46/375	2/38
	(16.55)	(0)	(12.27)	(5.26)
NEC, stage ≥ II	11/145	1/8	43/376	5/38
	(7.59)	(12.50)	(11.44)	(13.16)
ROP	101/134	7/8	235/314	24/31
	(75.37)	(87.50)	(74.84)	(77.42)
Severe ROP	11/134	0/8	90/314	6/31
	(8.21)	(0)	(28.66)	(19.35)
Discharge home on oxygen	73/143	4/8	274/371	29/37
	(51.05)	(50)	(73.85)	(78.38)
Number of transfusions,	0	0.5	3	2
median (IQR)	(0–1)	(0–1.75)	(0–5)	(0–4)
Total ventilation,days,	4	5	3	3
median (IQR)	(0–10)	(1–25)	(0–17)	(0–12)
Non-invasive resp. support,	50	60	20	22
Days, median (IQR)	(30–60)	(45–70)	(12–39)	(12–40)
Total suppl. Oxygen, days	75	75	150	140
median (IQR)	(40–90)	(50–100)	(100–250)	(100–180)
NICU stay, days,	85	110	80	70
median (IQR)	(75–120)	(80–135)	(65–105)	(60–95)

* Mann-Whitney U test for continuous variables which are not normally distributed, Chi-squared test for categorical variables and Fisher's exact test when the cell count <5

[a] Indicates statistical significance

Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise

The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroids; BPD: bronchopulmonary dysplasia; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the

membrane; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SNI: severe neurological injury
OR: odds ratio

In the DCC cohort, the group that completed follow-up had significantly lower incidences of maternal chorioamnionitis, PROM and PDA ligation compared to those lost to follow-up. In the ICC cohort, evaluated group had lower rates of maternal PIH, while the incidence of multiple births, PROM, and maternal antibiotic use was significantly higher compared to the lost to follow-up group. Furthermore, children in the evaluated group were more likely to be male and developed RDS during the early neonatal period with these differences reaching statistical significance.

Outcomes-specific results

Death or any Neurodevelopmental Impairments (NDIs)

The data on death or any NDIs were available for 431children, representing 76.01% of the total cohort (431 out of 567). Proportion of children with death or any NDI was higher in the DCC group compared to the ICC group (53.54% vs 38.55%). The unadjusted odds ratio was 1.84 (95% CI: 1.14–2.96) and the association reached statistical significance (p = .008); (**Table 50**).

Table 50. Association between DCC and death or any NDI at 36 months (n = 431)

Exposure	Death/ NDI (yes), n (%)	Death/NDI (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	53 (53.54)	46 (46.46)	99 (100)	1.15	1.84 (1.14–2.96)	.008[a]
ICC	128 (38.55)	204 (61.45)	332 (100)	0.63		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
NDI: neurodevelopmental impairment

Death or severe Neurodevelopmental Impairments (s-NDIs)

Data were available for 419 children, representing 73.90% of the total cohort (419 out of 567). The proportion of death or severe-NDI was 20% in the DCC and 20.68% in the ICC group. The unadjusted odds ratio was 0.96 (95% CI: 0.51–1.74); indicating not statistically significant (p = .885); (**Table 51**).

Table 51. Association between DCC and Death or s-NDI at 36 months (n = 419)

Exposure	Death/ s-NDI (yes), n (%)	Death/ s-NDI (no), n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	19 (20)	76 (80)	95 (100)	0.25	0.96 (0.51–1.74)	.885
ICC	67 (20.68)	257 (79.32)	324 (100)	0.26		

*p-value obtained using Chi-squared test
sNDI: severe neurodevelopmental impairment

Any Neurodevelopmental Impairments (NDIs)

Data on any NDI were available for 390 surviving children, 68.78% of the total cohort (390 out of 567). The proportion of children with NDI was relatively higher in the DCC group compared to the ICC group (47.73% vs 32.45%). The unadjusted odds ratio was 1.90 (95% CI: 1.14–3.17); and the association was statistically significant (p = .009); (**Table 52**).

Table 52. Association between DCC and any NDI at 36 months (n = 390)

Exposure	NDI (yes) n (%)	NDI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	42 (47.73)	46 (51.69)	88 (100)	0.91	1.90 (1.14–3.17)	.009[a]
ICC	98 (32.45)	204 (67.55)	302 (100)	0.48		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
NDI: neurodevelopmental impairment

Severe Neurodevelopmental Impairments (s-NDIs)

Data on severe NDI were available for 378 surviving children, representing 66.67% of the total cohort (378 out of 567). The proportion of severe NDI was relatively low in the DCC group than ICC (9.52% vs 12.59%). The unadjusted OR was 0.73 (95% CI: 0.28–1.68); however, the association was not statistically significant (p = .445); (**Table 53**).

Table 53. Association between DCC and severe NDI at 36 months (n = 378)

Exposure	s-NDI (yes) n (%)	s-NDI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	8 (9.52)	76 (90.48)	84 (100)	0.11	0.73 (0.28–1.68)	. 445
ICC	37 (12.59)	257 (87.41)	294 (100)	0.14		

*p-value obtained using Chi-squared test
s-NDI: severe neurodevelopmental impairment

Cerebral Palsy (CP)

Data were available for 377 surviving children, representing 66.49% of the total cohort (377 out of 567). The proportion of children diagnosed with CP of any grade was lower in DCC group compared to the ICC group (8.91% vs 10.87%). The unadjusted odds ratio was 0.80 (95% CI: 0.32–1.82) and the association was statistically significant (p= .580); (**Table 54**).

Table 54. Association between DCC and Cerebral palsy at 36 months (n = 377)

Exposure	CP (yes) n (%)	CP (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	9 (8.91)	92 (91.09)	101 (100)	0.10	0.80 (0.32–1.82)	.580
ICC	30 (10.87)	246 (89.13)	276 (100)	0.12		

*p-value obtained using Chi-squared test
CP: cerebral palsy

Table 55 compares severity of CP between the DCC and ICC groups. Among the 39 children diagnosed with CP, GMFCS data were available for 35 of them (89.74%). In the DCC, 2 children

(22.22%) had moderate and 7 (77.78%) had mild CP. In the ICC group, 4 children (15.38%) had severe, 10 (38.46%) had moderate CP and 12 (46.15%) had mild CP. The difference in CP severity between the groups was not statistically significant (p = .380).

Table 55. Comparison of the severity of cerebral palsy between DCC and ICC groups (n=35)

Severity of CP	**DCC Group (n = 9)**	**ICC Group (n = 26)**	**p-value***
Mild, n (%)	7 (77.78)	12 (46.15)	.380
Moderate, n (%)	2 (22.22)	10(38.46)	
Severe, n (%)	0 (0)	4 (15.39)	

*p-value obtained using Chi-squared test
CP: cerebral palsy

Cognitive Delay

The data on cognitive delay were available for 352 surviving children, representing 62.08% of the total cohort (352 out of 567 children). The proportion of children with cognitive delay was significantly higher in the DCC group compared to the ICC group (44.58% vs 23.79%, p= .001). The unadjusted odds ratio was 2.58 (95% CI: 1.48–4.45); indicating a statistically significant association (p = .001); (**Table 56**).

Table 56. Association between DCC and Cognitive Delay at 36 months (n = 352)

Exposure	**CD (yes) n (%)**	**CD (no) n (%)**	**Total n (%)**	**Odds (yes/no)**	**Odds Ratio (95% CI)**	**p-value***
DCC	37 (44.58)	46 (55.42)	83 (100)	0.80	2.58 (1.48–4.45)	.001[a]
ICC	64 (23.79)	205 (76.21)	269 (100)	0.24		

*p-value obtained using Chi-squared test
[a] Indicates statistical significance
CD: cognitive delay

Hearing Impairment

Data on hearing impairment were available for 351 children, representing 61.90% of the total cohort (351 out of 567 children). The proportion of children with hearing impairment differed significantly between the DCC and ICC groups (0% vs 6.15%, p= .015). Due to the absence of any cases of hearing impairment in the DCC group, an odds ratio could not be calculated; (**Table 57**).

Table 57. Association between DCC and hearing impairment at 36 months (n = 351)

Exposure	HI (yes) n (%)	HI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	0 (0)	91 (100)	91 (100)	0	N/A	.015[a]
ICC	16 (6.15)	244 (93.85)	260 (100)	0.07		

*p-value obtained using Fisher's exact test
[a] Indicates statistical significance
HI: hearing impairment

Visual Impairment

Data on visual impairment were available for 358 children, representing 63.14% of the total cohort (358 out of 567). The proportion of visual impairment was 3.23% in the DCC and 6.42% in the ICC group. The unadjusted odds ratio was 0.49 (95% CI: 0.09–1.74), however, the association did not reach statistical significance (p = .249); (**Table 58**).

Table 58. Association between DCC and visual Impairment at 36 months (n = 358)

Exposure	VI (yes) n (%)	VI (no) n (%)	Total n (%)	Odds (yes/no)	Odds Ratio (95% CI)	p-value*
DCC	3 (3.23)	90 (96.77)	93 (100)	0.03	0.49 (0.09–1.74)	.249
ICC	17 (6.42)	248 (93.58)	265 (100)	0.07		

*p-value obtained using Fisher's exact test
VI: visual impairment

Growth

Anthropometric measurements—weight, height, and head circumference were available for 33 children for SGA and 383 children classified as AGA. Two-sided independent t-tests were conducted to compare mean z-scores of growth parameters between the DCC and ICC groups. None of these parameters fell below −2 z-scores and no statistically significant differences were observed with DCC and ICC exposure, in either the SGA or AGA groups. These findings are illustrated in **Table 59**.

Table 59. Comparison of Growth at 36 months corrected age

Growth Parameter	SGA-DCC (n=10)	SGA-ICC (n=23)	p-value	AGA-DCC (n= 96)	AGA-ICC (n=287)	p-value
Weight z-score, mean (SD)	-1.26 (0.92)	-1.24 (0.90)	.962	-0.44 (1.02)	-0.25 (1.34)	.213
Height z-score, mean (SD)	-0.92 (1.24)	-1.04 (0.99)	.771	-0.35 (0.98)	-0.32 (1.22)	.848
Head circumference z-score, mean (SD)	-0.63 (1.21)	-1.13 (0.77)	.177	-0.04 (1.21)	-0.03 (0.77)	.945

*p-value obtained by two-sided t-test
DCC: deferred cord clamping; ICC: immediate cord clamping

Effect modification and confounding

Stratified Analysis

Stratified analyses were conducted to evaluate the influence of various maternal and neonatal factors as potential effect modifiers or confounders in the relationship between DCC and neurodevelopmental outcomes. Within each stratum of the third variable, odds ratios for the association between DCC exposure and neurodevelopmental outcomes were calculated. To assess whether the odds ratios differed significantly across strata, a test of homogeneity was

applied under the null hypothesis of equal odds ratios. A Wald test p-value < .05 indicated that the third variable acted as an effect modifier. If the homogeneity test was not significant, the crude odds ratio was compared with the Mantel-Haenszel (M-H) adjusted odds ratio to evaluate potential confounding. A difference of 10% or more between the crude and the Mantel-Haenszel (M-H) adjusted odds ratio was considered as a quantitative threshold to identify potential confounding (141), alongside consideration of the clinical relevance of the observed difference.

For maternal age and gestational age at birth, which were treated as continuous variable, box plots were generated against cord clamping status (DCC vs. ICC) as the primary grouping variable and death or neurodevelopmental impairments (NDIs) as a subgroup. Similar distributions of box plots across groups were interpreted as no effect modification or confounding. Conversely, noticeable differences in the box plots among the groups were considered indicative of potential effect modification or confounding.

To assess potential effect modification or confounding by birth weight and socioeconomic status, variables, birth weight, material and social deprivation quintiles were categorized. Birth weight was dichotomized at 870 grams, corresponding to the median birth weight of the study population. Material and social deprivation were grouped into two categories: quintiles 4 and 5 were classified as "deprived," while quintiles 1 to 3 were considered "not deprived." Stratified analyses based on these classifications were conducted to examine their potential influence on the relationship between DCC and long-term outcomes assessed at 18–24 months and 36 months corrected age.

This section presents the results of the stratified analyses conducted to assess the potential role of various maternal and neonatal factors as effect modifiers or confounders in the relationship between DCC and death or any NDIs at 18–24 and 36 months corrected age.

DCC and Death or any NDI at 18-24 months

The stratified analyses assessing the impact of maternal and neonatal characteristics between DCC and the composite outcome of death or any NDI, identified SGA and social deprivation as effect modifiers. The association was notably stronger among children who were SGA compared to those who were not. For variables where the homogeneity tests were not significant, the differences between crude and adjusted ORs were not found large enough to be considered them as confounding factors. These findings are presented in **Tables 60 – 63** and **Figures 14-15**).

Table 60. Effect of various maternal and neonatal characteristics on the association between DCC and death or any NDI at 18-24 months (n = 477)

Variables	Absent OR (95% CI)	Present OR (95% CI)	Test of Homogeneity (M-H) p-value*
Completion of high school	0.72 (0.17–3.37)	1.27 (0.75–2.19)	.402
PIH	1.23 (0.73–2.11)	1.89 (0.58–6.47)	.478
Gestational diabetes	1.49 (0.90–2.48)	0.42 (0.06–2.97)	.154
Chorioamnionitis	1.24 (0.73–2.09)	1.69 (0.57–5.69)	.582
C-section	1.77 (0.85–3.83)	0.99 (0.54–1.85)	.201
ANCS	0.61 (0.1–4.44)	1.43 (0.89–2.34)	.299
Maternal Antibiotic	1.24 (0.53–3.02)	1.27 (0.73–2.24)	.969
Multiparous	1.10 (0.59–2.08)	1.54 (0.76–3.20)	.451
Multiple Birth	1.20 (0.70–2.09)	1.55 (0.62–4.14)	.620
PROM	1.11 (0.65–1.92)	1.88 (0.74–5.09)	.302
Smoking	1.25 (0.77–2.05)	2.51 (0.47–25.19)	.412
Alcohol	1.31 (0.82–2.12)	0.56 (0.05–8.49)	.422

Male	1.25 (0.63–2.51)	1.30 (0.69–2.52)	.925
SGA	1.04 (0.65–1.70)	11 (1.24–504.28)	.035[a]
Apgar score <7	1.17 (0.68–2.02)	2.07 (0.76–6.58)	.303

*p-value obtained by Wald test
[a] Indicates statistical significance
ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; ICC: immediate cord clamping; PIH: pregnancy induced hypertension; PROM: premature rupture of the membrane; SGA: small for gestational age (<10th percentile)
OR: odds ratio

Table 61. Comparison between crude and adjusted odds ratio at 18-24 months (n= 477)

Variables	**Crude OR (95% CI)**	**M-H Combined OR (95% CI)**	**Difference (%) (Crude and AOR)**
Completion of high school	1.19 (0.72–1.96)	1.18 (0.74–1.89)	0.84
PIH	1.33 (0.83–2.15)	1.33 (0.85–2.10)	0
Gestational diabetes	1.33 (0.83–2.15)	1.35 (0.86–2.13)	1.5
Chorioamnionitis	1.29 (0.82–2.06)	1.32 (0.85–2.05)	2.3
C-section	1.28 (0.81–2.03)	1.27 (0.82–1.96)	0.78
ANCS	1.28 (0.81–2.04)	1.34 (0.87–2.08)	4.69
Maternal Antibiotic	1.28 (0.81–2.05)	1.26 (0.81–1.96)	1.56
Multiparous	1.28 (0.81–2.04)	1.28 (0.83–1.98)	0
Multiple Birth	1.28 (0.81–2.03)	1.29 (0.83–2)	0.78
PROM	1.28 (0.81–2.05)	1.28(0.83–1.98)	0
Smoking	1.28 (0.81–2.04)	1.33 (0.86–2.08)	3.91
Alcohol	1.28 (0.81–2.04)	1.27 (0.82–1.97)	0.78
Male	1.28 (0.81–2.03)	1.28 (0.82–1.98)	0
Apgar score at 5 min <7	1.29 (0.82–2.06)	1.35 (0.86–2.10)	4.65

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; ICC: immediate cord clamping; PIH: pregnancy induced hypertension; PROM: premature rupture of the membrane
AOR: adjusted odds ratio

Table 62. Assessment of effect modification by categorized birth weight, material and social deprivation between DCC and death or any NDI at 18-24 months (n = 477)

Variables (n = 477)	**Absent OR (95% CI)**	**Present OR (95% CI)**	**Test of homogeneity (M-H) p-value**
Birth weight (≥870 gram)	1.23 (0.62–2.54)	1.37 (0.72–2.62)	.814
Materially deprived (ref = 1,2,3)	1.72 (0.91–3.28)	0.82 (0.39–1.78)	.117
Socially deprived (ref = 1,2,3)	1.86 (0.87–2.75)	0.72 (0.34–1.54)	.043[a]

*p-value obtained by Wald test
[a] Indicates statistical significance
OR: odds ratio

Table 63. Assessment of Confounding factors by categorized birth weight and material deprivation between DCC and Death or any NDI at 18-24 months (n = 477)

Variables (n = 477)	Crude OR (95% CI)	M-H combined OR (95% CI)	Difference (%) crude and AOR
Birth weight (≥870 gram)	1.28 (0.81–2.03)	1.30 (0.84–2.03)	1.56
Materially deprived (ref = 1,2,3)	1.23 (0.77–1.99)	1.27 (0.81–1.99)	3.25

AOR: adjusted odds ratio

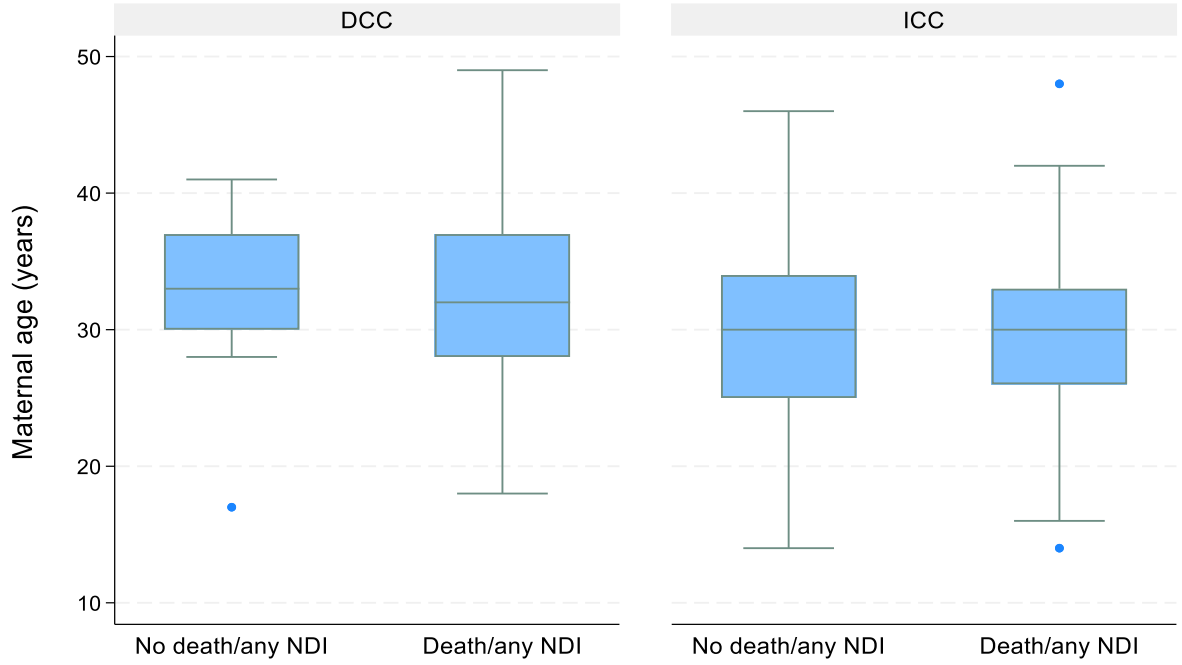

Figure 14. Comparison of box plots of maternal age in death or any NDI between groups at 18-24 months.

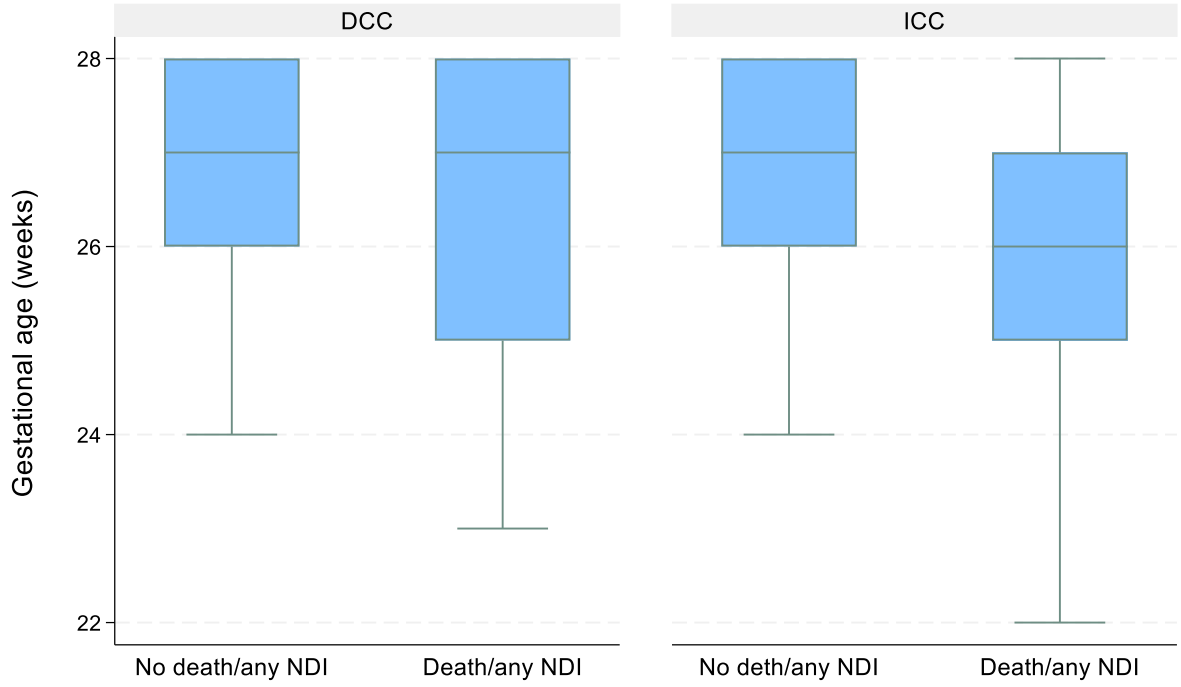

Figure 15. Comparison of box plots of gestational age in death or any NDI between groups at 18-24 months.

DCC and Death or any NDI at 36 months

Stratified analyses examining the influence of maternal and neonatal characteristics, on the association between DCC and the composite outcome of death or any NDI at 36 months revealed gestational diabetes as an effect modifier. On other variables, where homogeneity tests were not significant, the differences between the crude and Mantel-Haenszel adjusted odds ratios were not found substantial enough to be considered them as confounding factors. These findings are presented in (**Tables 64 – 67 and Figures 16-17**).

Table 64. Effect of various maternal and neonatal characteristics on the association between DCC and death or any NDI at 36 months (n = 431)

Variables	Absent OR (95% CI)	Present OR (95% CI)	Test of Homogeneity (M-H) p-value*
Completion of high school	1.27 (0.19–9.73)	1.89 (1.05–3.35)	.649
PIH	1.38 (0.79–2.39)	4.11 (1.07–17.37)	.104
Gestational diabetes	2.04 (1.21–3.43)	0.06 (0.001–0.97)	.006[a]
Chorioamnionitis	2.05 (1.17–3.58)	1.71 (0.59–5.21)	.744
C-section	1.46 (0.71–2.99)	2.15 (1.10–4.21)	.402
ANCS	4.22 (0.44–204.22)	1.95 (1.18–3.23)	.499
Maternal Antibiotic	4.19 (1.51–12.70)	1.41 (0.80–2.50)	.050
Multiparous	2.55 (1.27–5.16)	1.31 (0.65–2.62)	.153
Multiple Birth	1.69 (0.95–2.98)	2.28 (0.88–6.01)	.559
PROM	1.87 (1.04–3.37)	1.91 (0.78–4.63)	.965
Smoking	1.87 (1.12–3.11)	1.62 (0.20–12.85)	.872
Alcohol	1.91 (1.17–3.11)	1.60 (0.07–106.02)	.896
Male	1.25 (0.59–2.59)	2.57 (1.32–5.09)	.124
SGA	1.55 (0.92–2.58)	6.42 (1.14–44.21)	.085
Apgar score at 5 min <7	2.02 (1.08–3.76)	1.54 (0.69–3.52)	.576

*p-value obtained by Wald test
[a] Indicates statistical significance
ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; ICC: immediate cord clamping PIH: pregnancy induced hypertension, PROM: premature rupture of the membrane, SGA = small for gestational age (<10th percentile)
OR: odds ratio

Table 65. Comparison between crude and adjusted odds ratio at 36 months (n = 431)

Variables	Crude OR (95% CI)	M-H Combined OR (95% CI)	Difference (%) (Cude and AOR)
Completion of high school	1.71 (0.99–2.93)	1.81 (1.08–3.02)	5.85
PIH	1.67 (1.02–2.75)	1.65 (1.03–2.64)	1.20
Chorioamnionitis	1.89 (1.16–3.06)	1.96 (1.24–3.12)	3.70

C-section	1.84 (1.14–2.96)	1.79 (1.14–2.81)	2.72
ANCS	1.87 (1.16–3.01)	2.05 (1.29–3.25)	9.63
Maternal Antibiotic	1.84 (1.14–2.97)	1.87 (1.19–2.96)	1.63
Multiparous	1.83 (1.13–2.96)	1.82 (1.16–2.86)	0.55
Multiple Birth	1.84 (1.14–2.96)	1.83 (1.16–2.88)	0.54
PROM	1.87 (1.16–3.02)	1.88 (1.19–2.97)	0.535
Smoking	1.85 (1.15–2.99)	1.85 (1.17–2.93)	0
Alcohol	1.87 (1.15–2.99)	1.89 (1.20–2.98)	1.07
Male	1.84 (1.14–2.96)	1.85 (1.18–2.91)	.543
SGA	1.84 (1.14–2.96)	1.78 (1.13–2.81)	3.26
Apgar score at 5 min <7	1.87 (1.16–3.02)	1.82 (1.15–2.88)	2.67

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; ICC: immediate cord clamping; PIH: pregnancy induced hypertension, PROM: premature rupture of the membrane, SGA: small for gestational age (<10th percentile)
AOR: adjusted odds ratio

Table 66. Assessment of effect modification between DCC and Death or any NDI by categorized birth weight, material and social deprivation at 36 months (n = 431)

Variables	**Absent OR (95% CI)**	**Present OR (95% CI)**	**Test of homogeneity (M-H) p-value***
Birth weight (≥870 gram)	1.98 (0.91–4.34)	1.81 (0.96–3.41)	.855
Materially deprived (ref = 1,2,3)	1.95 (0.98–3.84)	2.27 (1.02–5.28)	.763
Socially deprived (ref = 1,2,3)	1.73(0.91–3.30)	2.12 (0.93–4.86)	.681

*p-value obtained by Wald test
OR: odds ratio

Table 67. Assessment of confounding factors by categorized birth weight, material and social deprivation between DCC and Death or any NDI at 36 months (n = 431)

Variables	Crude OR (95% CI)	M-H combined OR (95% CI)	Difference (%) (crude and AOR)
Birth weight (≥870 gram)	1.84 (1.14–2.96)	1.88 (1.19–2.96)	2.17
Materially deprived (ref = 1,2,3)	1.91 (1.17–3.13)	2.08 (1.28–3.37)	8.90
Socially deprived (ref = 1,2,3)	1.91 (1.17–3.13)	1.87 (1.17–2.99)	2.09

AOR: adjusted odds ratio

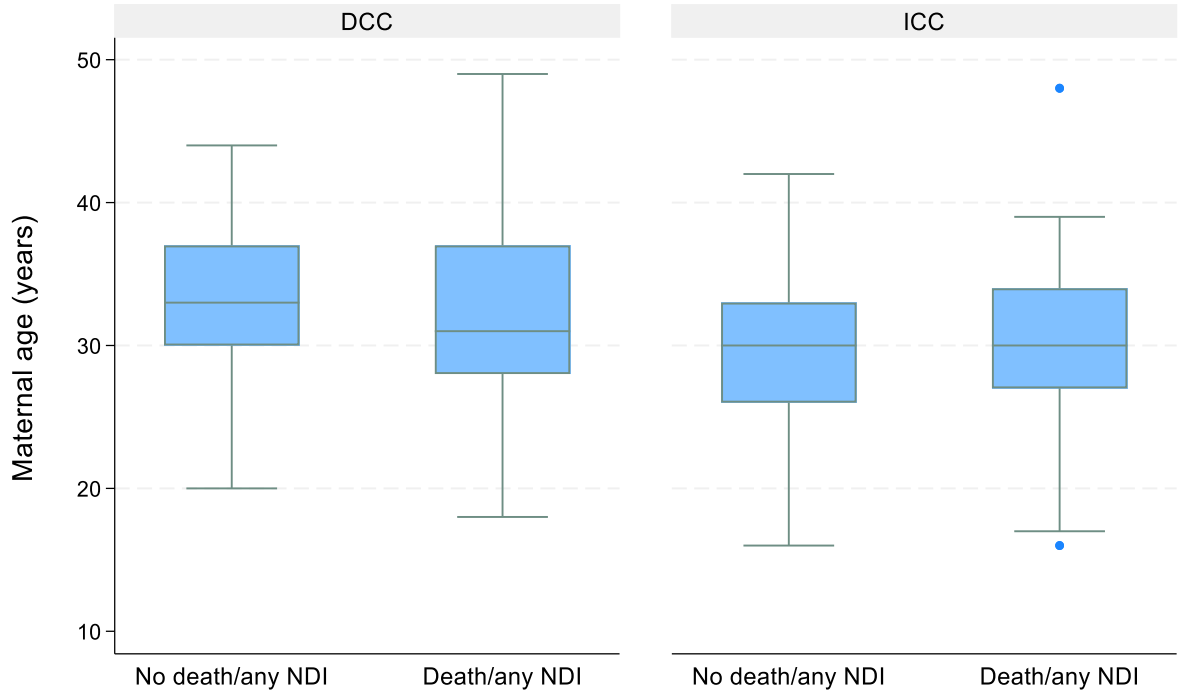

Figure 16. Comparison of box plots of maternal age in death or any NDI between DCC and ICC groups at 36 months.

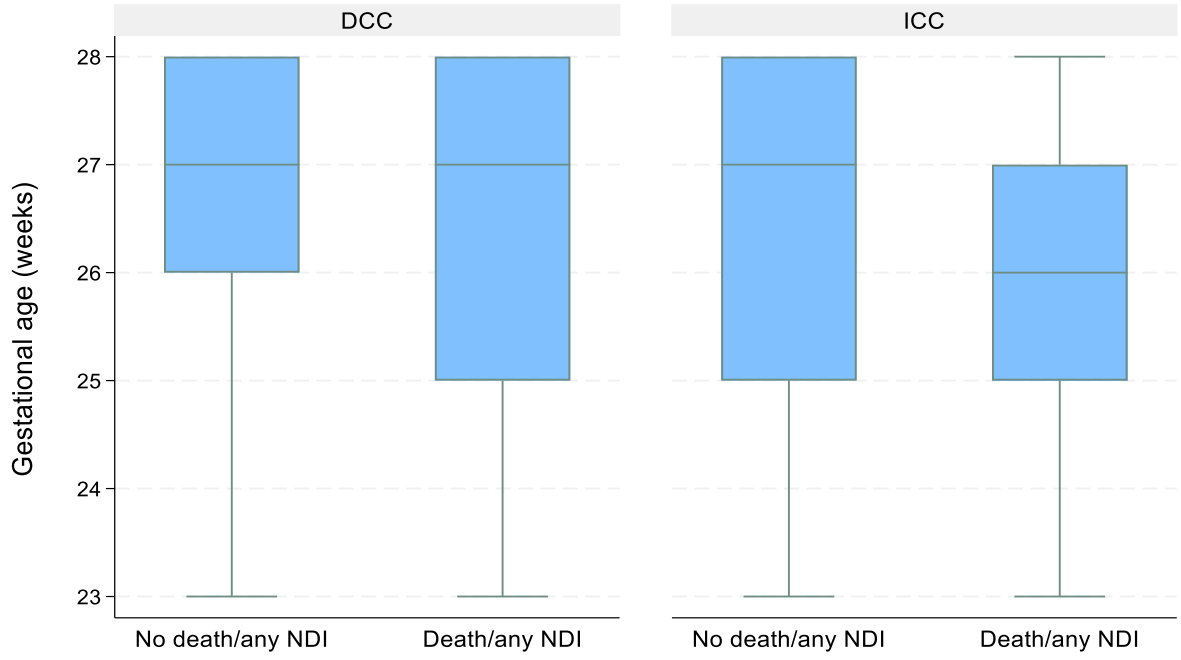

Figure 17. Comparison of box plots of gestational age in death or any NDI between DCC and ICC groups at 36 months.

Logistic Regression

Model Building

The goal of the multivariable logistic regression analysis was to develop the best fitting model to describe the relationship between the exposure and outcomes of interest, while adjusting for relevant maternal and neonatal predictors or explanatory variables (covariates).

Multicollinearity Assessment:

Collinearity among independent variables was assessed using matrix of correlation. Correlation matrix is a tool indicates the correlations between each pair of explanatory variables using the square root of R2. Values close to 1 indicates that variables were strongly associated with each other and multicollinearity may be a problem. A correlation coefficient (r) of more than 0.6 was considered significant. A strong positive correlation was observed between gestational age and

birth weight (r = 0.65; p < .001). Moderate correlations were found among chorioamnionitis, maternal antibiotic administration, and prolonged rupture of membranes (r=0.30), as well as between maternal smoking and alcohol consumption during pregnancy (r = 0.29). A weak negative correlation was found between maternal education and material deprivation (r = -0.15).

Choosing variables in the Model:

Variable selection was guided primarily by the magnitude of change between crude and adjusted odds ratios, rather than relying solely on statistical significance (p-values). To ensure the inclusion of all relevant covariates and to minimize residual confounding , a variable was considered for inclusion in the model if it resulted in a substantial change in the effect estimate (i.e., difference in ORs, ≥10%) (141) . This approach yielded more robust and reliable models than methods based solely on statistical significance thresholds (p < .05). Additionally, variables previously identified as confounders in the literature were given strong consideration for inclusion in the final model.

Primarily, covariates showing a statistically significant difference (p <.05) between the DCC and ICC groups were identified as potential confounders (170). However, to be classified as a confounding variable, covariates had to meet specific criteria; they must be correlated with the exposure, be a direct cause of outcome or a surrogate for a direct cause of the outcome and must not lie on the causal pathway between exposure and outcome. Recent, research has emphasized that a confounding variable cannot be a one that is affected by the exposure (171, 172).

Maternal age, ANCS, antibiotic use during labour, smoking in pregnancy, material deprivation quintiles, GA and SGA were identified as potential confounders from univariate analysis based on statistical significance (p<.05).

From stratified analysis, using the rule of substantial change (≥10%) in effect estimates, no variables were identified as potential confounder.

In previous studies examining deferred cord clamping and neurodevelopmental impairment, researchers have adjusted for a range of maternal and perinatal factors, including maternal education, PIH, chorioamnionitis, multiple birth, C-section, ANCS and antibiotic use, PROM, smoking, alcohol consumption, socioeconomic status, GA, male sex, Apgar score at 5 minutes<7, SGA (122, 173-176).

Gestational age and birth weight are the well-known predictors of neurodevelopmental outcomes of infants born prematurely. As mentioned previously, gestational age and birth weight were collinear. Gestational age was selected over birth weight because most neurodevelopmental studies have used gestational age as the primary predictor of long-term neurodevelopmental outcomes. Moreover, heavier newborns generally act more like peers of the same gestational age than like infants with similar weights.

Collinearity was also observed among the variables chorioamnionitis, maternal antibiotic administration, and prolonged rupture of the membrane; between smoking and alcohol consumption during pregnancy; and between material deprivation and maternal education. Based on expert opinion, chorioamnionitis, smoking and material deprivation were selected as confounders for adjustment in the analysis.

Of all the covariates identified through our selection approach, the following met the definition of confounding: maternal age, PIH, gestational diabetes, chorioamnionitis, ANCS, C-section, multiple birth, smoking, GA, male sex, SGA, Apgar score at 5 minutes<7 and socioeconomic status (material and social deprivation).

Logistic regression analysis began by assessing effect modification through the inclusion of interaction terms (exposure × covariate) for variables identified as potential effect modifiers in the stratified analysis. Covariates with statistically significant interaction terms ($p < .05$) were treated as effect modifiers. Interaction term that did not reach statistical significance, was excluded from the final model.

The final logistic regression analysis includes all covariates that met the definition of confounding. Each model for neurodevelopment outcomes was evaluated for goodness of fit by using the Hosmer-Lemeshow test. As separate cohorts of infants were used for the DCC and ICC periods, the application of this test was appropriate for evaluating model's fit. A high p-value suggested that the differences between the observed and predicted event rates across the groups were not statistically significant, indicating that the model provided a good fit to the data.

Regression Analysis for 18-24 Months Follow-Up

DCC and Death or any NDI

Interaction terms between cord clamping and two potential effect modifiers, SGA and social deprivation (ref = 1,2,3), were included in the logistic regression model following identification through stratified analysis. However, neither interaction reached statistical significance, therefore, both terms were excluded from the model.

The adjusted odds ratio for DCC and death or any NDI was 1.77; 95% CI: 1.04–3.02, $p = .034$. The model demonstrated adequate fit to the data according to the Hosmer–Lemeshow test ($p = .377$).

Table 68. Adjusted odds ratio for death or any NDI as a function of DCC at 18-24 months (n = 347)

Death or any NDI	OR	Std. err.	Z	P>|z|	95% CI
DCC (ref = ICC)	1.77	0.48	2.12	.034[a]	1.04–3.02
Maternal age	0.98	0.02	-0.78	.437	0.94–1.03
PIH (ref = no PIH)	0.88	0.32	-0.36	.719	0.43–1.79
Gestational Diabetes (ref = no gestational diabetes)	0.76	0.37	-0.55	.583	0.29–1.99
Chorioamnionitis (ref = no chorioamnionitis)	1.93	0.58	2.19	.029[a]	1.07–3.49
C-section (ref = vaginal delivery)	1.06	0.29	0.23	.816	0.63–1.80
ANCS (ref = not received ANCS)	0.64	0.26	-1.08	.282	0.28–1.44
Multiple birth (ref = singleton pregnancy)	1.37	0.30	1.46	.144	0.90–2.10
Smoking (ref = no smoking while pregnant)	1.07	0.36	0.21	.832	0.55–2.09
GA	0.78	0.07	-2.76	.006[a]	0.65–0.93
Male (ref = female)	1.14	0.28	0.54	.586	0.71–1.84
Apgar score at 5 minutes <7 (ref = Apgar score at 5 minutes≥7)	2.49	0.69	3.30	.001[a]	1.45–4.28
SGA (ref = no SGA)	3.55	1.68	2.68	.007[a]	1.41–8.96
Materially deprived (ref = 1,2,3)	1.60	0.40	1.88	.060	0.98–2.61
Socially deprived (ref =1, 2,3)	1.30	0.32	1.06	.289	0.80–2.10

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)

[a] Indicates statistical significance

Death / any NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 205.82, LR chi2 (15) = 50.32, Prob>chi2: <.001

DCC and Death or severe NDI

The adjusted odds ratio for DCC and death or severe NDI was 1.24; 95% CI: 0.67–2.29, p = .487. The model demonstrated adequate fit to the data according to the Hosmer–Lemeshow test (p=.063).

Table 69. Adjusted odds ratio for death or severe NDI as a function of DCC at 18-24 months (n = 321)

Death or severe NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.24	0.39	0.70	.487	0.67–2.29
Maternal age	0.99	0.03	-0.17	.863	0.94–1.05
PIH (ref = no PIH)	1.96	0.86	1.55	.121	0.84–4.62
Gestational Diabetes (ref = no gestational diabetes)	1.25	0.72	0.40	.691	0.41–3.84
Chorioamnionitis (ref = no chorioamnionitis)	1.57	0.51	1.39	.165	0.83–2.98
C-section (ref = vaginal delivery)	1.06	0.33	0.20	.842	0.58–1.96
ANCS (ref = not received ANCS)	0.46	0.19	-1.84	.066	0.20–1.05
Multiple birth (ref = singleton pregnancy)	1.49	0.36	1.67	.096	0.93–2.40
Smoking (ref = no smoking while pregnant)	0.80	0.32	-0.57	.570	0.37–1.74
GA	0.68	0.07	-3.95	<.001[a]	0.56–0.82
Male (ref = female)	1.90	0.55	2.22	.027[a]	1.08–3.34
Apgar score at 5 minutes <7 (ref = Apgar score at 5 minutes≥7)	2.23	0.66	2.70	.007[a]	1.25–3.98
SGA (ref = no SGA)	1.15	0.57	0.28	.779	0.43–3.03
Materially deprived (ref = 1,2,3)	1.07	0.31	0.25	.802	0.61–1.89

Socially deprived (ref =1, 2,3)	1.25	0.35	0.80	.424	0.72–2.19

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Death / severe NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 164.45, LR chi2 (15) = 44.21, Prob>chi2: .001

DCC and any NDI

The adjusted odds ratio for DCC and any NDI was 1.70; 95% CI: 0.99–2.92, p = .055. The model demonstrated adequate fit to the data according to the Hosmer–Lemeshow test (p = .282)

Table 70. Adjusted odds ratio for any NDI as a function of DCC at 18-24 months (n = 318)

Any NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.70	0.47	1.92	.055	0.99–2.92
Maternal age	0.98	0.02	-0.73	.466	0.94–1.03
PIH (ref = no PIH)	0.90	0.33	-0.29	.770	0.44–1.84
Gestational Diabetes (ref = no gestational diabetes)	0.73	0.37	-0.62	.532	0.27–1.96
Chorioamnionitis (ref = no chorioamnionitis)	1.98	0.61	2.22	.027[a]	1.08–3.61
C-section (ref = vaginal delivery)	1.03	0.28	0.12	.906	0.60–1.77
ANCS (ref = not received ANCS)	0.77	0.34	-0.58	.560	0.33–1.83
Multiple birth (ref = singleton pregnancy)	1.41	0.31	1.56	.120	0.92–2.16
Smoking (ref = no smoking while pregnant)	1.12	0.38	0.33	.740	0.57–2.20
GA	0.84	0.08	-1.81	.071	0.69–1.01
Male (ref = female)	1.12	0.28	0.47	.640	0.69–1.83

Apgar score at 5 minutes <7 (ref = Apgar score at 5 minutes≥7)	2.32	0.66	2.96	.003[a]	1.33–4.06
SGA (ref = no SGA)	2.97	1.43	2.27	.023[a]	1.16–7.62
Materially deprived (ref = 1,2,3)	1.67	0.42	2.01	.044[a]	1.01–2.74
Socially deprived (ref =1, 2,3)	1.36	0.34	1.22	.223	0.83–2.22

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Any NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 196.37, LR chi2 (15) = 39.56, Prob>chi2: .001

DCC and severe NDI

The adjusted odds ratio for DCC and severe NDI was 1.05; 95% CI: 0.51–2.13, p = .897. The model demonstrated adequate fit to the data according to the Hosmer–Lemeshow test (p = .074)

Table 71. Adjusted odds ratio for severe NDI as a function of DCC at 18-24 months (n = 292)

Severe NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.05	0.38	0.13	.897	0.51–2.13
Maternal age	0.99	0.03	-0.12	.906	0.94–1.06
PIH (ref = no PIH)	2.05	1.02	1.43	.152	0.77–5.46
Gestational Diabetes (ref = no gestational diabetes)	1.23	0.81	0.32	.748	0.34–4.47
Chorioamnionitis (ref = no chorioamnionitis)	1.88	0.69	1.71	.086	0.91–3.87
C-section (ref = vaginal delivery)	0.90	0.31	-0.31	.753	0.45–1.77
ANCS (ref = not received ANCS)	0.64	0.33	-0.85	.396	0.23–1.78
Multiple birth (ref = singleton pregnancy)	1.92	0.51	2.46	.014[a]	1.14–3.23
Smoking	0.85	0.38	-0.37	.713	0.35–2.03

(ref = no smoking while pregnant)					
GA	0.79	0.09	-2.01	.045[a]	0.62–0.99
Male (ref = female)	2.12	0.71	2.23	.026[a]	1.09–4.11
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	2.16	0.75	2.21	.027[a]	1.09–4.27
SGA (ref = no SGA)	0.45	0.32	-1.14	.256	0.11–1.79
Materially deprived (ref = 1,2,3)	1.19	0.39	0.52	.600	0.62–2.27
Socially deprived (ref =1, 2,3)	1.45	0.48	1.13	.260	0.76–2.78

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Severe NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 130.40, LR chi2 (15) = 27.52, Prob>chi2: .025

DCC and cerebral palsy

The adjusted odds ratio for DCC and cerebral palsy was 1.06; 95% CI: 0.39–2.89, p = .908. The Hosmer-Lemeshow test yielded a p-value of .049, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 72. Adjusted odds ratio for CP as a function of DCC at 18-24 months (n = 226)

Cerebral Palsy	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.06	0.54	0.12	.908	0.39–2.89
Maternal age	1.03	0.04	0.78	.435	0.96–1.11
PIH (ref = no PIH)	1.51	1.03	0.61	.545	0.40–5.75
Gestational Diabetes (ref = no gestational diabetes)	1.85	1.57	0.72	.469	0.35–9.77

Chorioamnionitis (ref = no chorioamnionitis)	2.26	1.20	1.53	.126	0.80–6.39
C-section (ref = vaginal delivery)	0.80	0.39	-0.46	.644	0.31–2.07
ANCS (ref = not received ANCS)	0.46	0.32	-1.11	.267	0.12–1.81
Multiple birth (ref = singleton pregnancy)	1.29	0.50	0.66	.507	0.61–2.76
Smoking (ref = no smoking while pregnant)	1.36	0.80	0.52	.602	0.43–4.32
GA	0.80	0.13	-1.37	.170	0.58–1.10
Male (ref = female)	2.01	0.94	1.50	.134	0.81–5.02
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	5.06	2.39	3.43	.001[a]	2.01–12.78
SGA (ref = no SGA)	0.72	0.91	-0.26	.796	0.06–8.41
Materially deprived (ref = 1,2,3)	2.37	1.01	1.84	.066	0.95–5.93
Socially deprived (ref =1, 2,3)	0.52	0.25	-1.35	.178	0.20–1.35

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Cerebral palsy adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 71.92, LR chi2 (15) = 33.14, Prob>chi2: .005

DCC and cognitive delay

The adjusted odds ratio for DCC and cognitive delay was 0.89; 95% CI: 0.43–1.85; p = .764. The Hosmer-Lemeshow test yielded a p-value of .023, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 73. Adjusted odds ratio for cognitive delay as a function of DCC at 18-24 months (n = 240)

Cognitive delay	OR	Std. err.	Z	P>|z|	95% CI
DCC (ref = ICC)	0.89	0.33	-0.30	.764	0.43–1.85
Maternal age	0.98	0.03	-0.50	.616	0.93–1.05
PIH (ref = no PIH)	1.38	0.70	0.64	.520	0.51–3.72
Gestational Diabetes (ref = no gestational diabetes)	1.56	1.06	0.65	.512	0.41–5.90
Chorioamnionitis (ref = no chorioamnionitis)	2.75	1.07	2.59	.010[a]	1.28–5.91
C-section (ref = vaginal delivery)	0.97	0.36	-0.08	.937	0.46–2.02
ANCS (ref = not received ANCS)	0.53	0.31	-1.10	.272	0.17–1.65
Multiple birth (ref = singleton pregnancy)	1.28	0.37	0.84	.403	0.72–2.26
Smoking (ref = no smoking while pregnant)	0.95	0.44	-0.11	.909	0.38–2.35
GA	0.73	0.09	-2.48	.013[a]	0.57–0.94
Male (ref = female)	2.12	0.75	2.13	.033[a]	1.06–4.24
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	1.80	0.68	1.56	.118	0.86–3.77
SGA (ref = no SGA)	3.95	2.50	2.17	.030[a]	1.14–13.67
Materially deprived (ref = 1,2,3)	1.49	0.50	1.17	.243	0.76–2.89
Socially deprived (ref =1, 2,3)	1.09	0.37	0.26	.794	0.56–2.11

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)

[a] Indicates statistical significance

Cognitive delay adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 118.13, LR chi2 (15) = 33.67, Prob>chi2: .004

DCC and motor delay

The adjusted odds ratio for DCC and motor delay was 1.86; 95% CI: 0.99–3.50, p = .054. The Hosmer- Lemeshow test indicated that there was no significant difference between expected frequencies and observed frequencies for the motor delay outcome, suggesting that the final model was a good fit (p = .091).

Table 74. Adjusted odds ratio for motor delay as a function of DCC at 18-24 months (n = 245)

Motor delay	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.86	0.60	1.93	.054	0.99–3.50
Maternal age	0.99	0.03	-0.23	.821	0.94–1.05
PIH (ref = no PIH)	0.85	0.38	-0.36	.717	0.35–2.06
Gestational Diabetes (ref = no gestational diabetes)	0.97	0.55	-0.05	.962	0.32–2.96
Chorioamnionitis (ref = no chorioamnionitis)	1.58	0.57	1.26	.207	0.78–3.19
C-section (ref = vaginal delivery)	1.02	0.32	0.06	.952	0.54–1.90
ANCS (ref = not received ANCS)	0.85	0.47	-0.29	.769	0.28–2.55
Multiple birth (ref = singleton pregnancy)	1.50	0.39	1.56	.118	0.90–2.49
Smoking (ref = no smoking while pregnant)	1.20	0.49	0.44	.661	0.53–2.68
GA	0.76	0.08	-2.50	.013[a]	0.61–0.94
Male (ref = female)	1.77	0.54	1.87	.062	0.97–3.22
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	2.63	0.90	2.82	.005[a]	1.34–5.15
SGA (ref = no SGA)	3.80	2.20	2.31	.021[a]	1.22–11.81
Materially deprived (ref = 1,2,3)	1.46	0.44	1.27	.206	0.81–2.63
Socially deprived (ref =1, 2,3)	1.23	0.37	0.67	.501	0.68–2.22

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Motor delay adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 140.99, LR chi2 (15) = 35.56, Prob>chi2: .002

DCC and language delay

The adjusted odds ratio for DCC and language delay was 1.39; 95% CI: 0.78–2.49, p = .265. The Hosmer- Lemeshow test indicated no significant difference between expected and observed frequencies of the language delay outcome, suggesting that the final model was a good fit (p = .141).

Table 75. Adjusted odds ratio for language delay as a function of DCC at 18-24 months (n = 278)

Language delay	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	1.39	0.41	1.11	.265	0.78–2.49
Maternal age	0.99	0.02	-0.42	.672	0.94–1.04
PIH (ref = no PIH)	1.07	0.42	0.18	.856	0.50–2.31
Gestational Diabetes (ref = no gestational diabetes)	0.84	0.46	-0.32	.747	0.29–2.45
Chorioamnionitis (ref = no chorioamnionitis)	2.12	0.70	2.28	.023[a]	1.11–4.03
C-section (ref = vaginal delivery)	1.14	0.34	0.44	.662	0.64–2.03
ANCS (ref = not received ANCS)	0.64	0.29	-0.97	.333	0.26–1.58
Multiple birth (ref = singleton pregnancy)	1.65	0.38	2.14	.032[a]	1.04–2.60
Smoking (ref = no smoking while pregnant)	1.24	0.43	0.63	.527	0.63–2.43
GA	0.84	0.08	-1.72	.086	0.69–1.02
Male (ref = female)	1.21	0.32	0.70	.484	0.71–2.03

Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	1.95	0.58	2.26	.024[a]	1.09–3.50
SGA (ref = no SGA)	3.73	1.89	2.60	.009[a]	1.38–10.08
Materially deprived (ref = 1,2,3)	1.76	0.48	2.11	.035[a]	1.04–2.99
Socially deprived (ref =1, 2,3)	1.26	0.33	0.89	.374	0.75–2.12

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Language delay adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 174.43, LR chi2 (15) = 35.55, Prob>chi2: .002

DCC and hearing impairment

The model did not fit for hearing impairment due to the absence of events in the DCC group.

DCC and visual impairment

The adjusted odds ratio for DCC and visual impairment was 0.07; 95% CI: 0.002–2.20, p = .129. The Hosmer- Lemeshow test indicated that no significant difference between expected and observed frequencies of visual impairment outcome, suggesting the final model was a good fit (p = .999).

Table 76. Adjusted odds ratio for visual impairment as a function of DCC at 18-24 months (n=194)

Visual Impairment	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	.07	0.12	-1.52	.129	0.002–2.20
Maternal age	1.08	0.12	0.71	.477	0.87–1.33
PIH (ref = no PIH)	13.50	24.55	1.43	.153	0.38–477.41
Gestational Diabetes	10.15	21.37	1.10	.271	0.16–629.24

(ref = no gestational diabetes)					
Chorioamnionitis (ref = no chorioamnionitis)	5.15	7.59	1.11	.266	0.29–92.47
C-section (ref = vaginal delivery)	0.13	0.17	-1.54	.123	0.01–1.74
Multiple birth (ref = singleton pregnancy)	3.62	3.34	1.40	.162	0.59–22.04
Smoking (ref = no smoking while pregnant)	1.06	1.35	0.04	.966	0.09–13.02
GA	0.25	0.14	-2.51	.012[a]	0.08–1.10
Male (ref = female)	1.62	1.75	0.44	.657	0.81–0.74
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	12.04	12.85	2.33	.020[a]	0.19–13.56
SGA (ref = no SGA)	22.48	45.32	1.54	.123	1.49–97.54
Materially deprived (ref = 1,2,3)	2.06	2.40	0.62	.533	0.43–1169.48
Socially deprived (ref =1, 2,3)	1.50	1.44	0.42	.675	0.21–9.87

C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)

[a] Indicates statistical significance

Visual impairment adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = -19.50, LR chi2 (14) = 39.79, Prob>chi2: .001

Regression Analysis for 36 Months Follow-Up

DCC and Death or any NDI

An interaction term between cord clamping and gestational diabetes was included into the logistic regression model to evaluate potential effect modification by gestational diabetes following identification through stratified analysis. However, this interaction did not reach statistical significance, and was therefore, excluded from the final model for parsimony.

The adjusted odds ratio for DCC and death or any NDI was 2.24; 95% CI: 1.23–4.09, p = .009. The Hosmer-Lemeshow test yielded a p-value of .036, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 77. Adjusted odds ratio for death or any NDI as a function of DCC at 36 months (n = 279)

Death/any NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	2.24	0.69	2.62	.009	1.23–4.09
Maternal age	1.01	0.03	0.41	.683	0.96–1.06
PIH (ref = no PIH)	2.45	1.04	2.11	.035[a]	1.07–5.64
Gestational Diabetes (ref = no gestational diabetes)	0.67	0.42	-0.63	.529	0.20–2.31`
Chorioamnionitis (ref = no chorioamnionitis)	2.29	0.78	2.43	.015[a]	1.18–4.46
C-section (ref = vaginal delivery)	0.97	0.29	-0.10	.923	0.54–1.75
ANCS (ref = not received ANCS)	0.47	0.23	-1.52	.128	0.18–1.24
Multiple birth (ref = singleton pregnancy)	1.67	0.52	1.65	.099	0.91–3.08
Smoking (ref = no smoking while pregnant)	0.67	0.27	-0.99	.322	0.30–1.48
GA	0.84	0.09	-1.66	.096	0.69–1.03
Male (ref = female)	1.78	0.50	2.07	.038[a]	1.03–3.09
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	1.64	0.49	1.64	.102	0.91–2.95
SGA (ref = no SGA)	1.28	0.66	0.48	.632	0.46–3.53
Materially deprived (ref = 1,2,3)	2.72	0.76	3.56	<.001[a]	1.57–4.71
Socially deprived (ref =1, 2,3)	0.86	0.24	-0.52	.601	0.49–1.50

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance

Death / any NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 163.92, LR chi2 (15) = 47.22, Prob>chi2: < .001

DCC and Death or severe NDI

The adjusted odds ratio for DCC and death or severe NDI was 0.61; 95% CI: 0.24–1.54, p = .293. The Hosmer- Lemeshow test indicated that no significant difference between expected and observed frequencies of death or severe NDI outcome, suggesting that the final model was a good fit (p = .508)

Table 78. Adjusted odds ratio for death or severe NDI as a function of DCC at 36 months (n = 269)

Death/severe NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	0.61	0.29	-1.05	.293	0.24–1.54
Maternal age	1.05	0.04	1.37	.172	0.98–1.13
PIH (ref = no PIH)	2.92	1.70	1.84	.066	0.93–9.14
Gestational Diabetes (ref = no gestational diabetes)	2.22	1.77	1.00	.317	0.47–10.56
Chorioamnionitis (ref = no chorioamnionitis)	1.22	0.59	0.42	.678	0.47–3.15
C-section (ref = vaginal delivery)	0.69	0.30	-0.84	.400	0.29–1.64
ANCS (ref = not received ANCS)	0.74	0.49	-0.46	.642	0.20–2.68
Multiple birth (ref = singleton pregnancy)	1.25	0.59	0.47	.635	0.50–3.15
Smoking (ref = no smoking while pregnant)	0.85	0.46	-0.31	.757	0.29–2.44
GA	0.97	0.14	-0.22	.822	0.73–1.29
Male (ref = female)	0.72	0.29	-0.82	.411	0.33–1.58
Apgar score at 5 minutes <7	3.18	1.35	2.72	.006[a]	1.38–7.30

(ref = Apgar score at 5minutes≥7)					
SGA (ref = no SGA)	0.26	0.29	-1.20	.228	0.03–2.33
Materially deprived (ref = 1,2,3)	2.08	0.87	1.75	.079	0.92–4.71
Socially deprived (ref =1, 2,3)	1.50	0.61	0.99	.322	0.67–3.35

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Death / severe NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = -90.09 LR chi2 (15) = 23.97, Prob>chi2: .066

DCC and any NDI

The adjusted odds ratio for DCC and any NDI was 2.28; 95% CI: 1.25–4.18, p = .007. The Hosmer-Lemeshow test yielded a p-value of .036, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 79. Adjusted odds ratio for any NDI as a function of DCC at 36 months (n = 278)

Any NDI	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	2.28	0.70	2.68	.007[a]	1.25–4.18
Maternal age	1.01	0.03	0.20	.844	0.95–1.06
PIH (ref = no PIH)	2.51	1.07	2.16	.031[a]	1.09–5.79
Gestational Diabetes (ref = no gestational diabetes)	0.69	0.43	-0.59	.555	0.20–2.37`
Chorioamnionitis (ref = no chorioamnionitis)	2.30	0.78	2.45	.014[a]	1.18–4.47
C-section (ref = vaginal delivery)	0.96	0.29	-0.14	.888	0.53–1.73
ANCS (ref = not received ANCS)	0.52	0.26	-1.29	.197	0.19–1.41

Multiple birth (ref = singleton pregnancy)	1.62	0.51	1.54	.123	0.88–3.00
Smoking (ref = no smoking while pregnant)	0.69	0.28	-0.94	.349	0.31–1.51
GA	0.84	0.09	-1.73	.084	0.68–1.02
Male (ref = female)	1.83	0.52	2.15	.032[a]	1.06–3.18
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	1.59	0.48	1.54	.123	0.88–2.89
SGA (ref = no SGA)	1.28	0.66	0.48	.632	0.47–3.52
Materially deprived (ref = 1,2,3)	2.64	0.74	3.45	.001[a]	1.52–4.59
Socially deprived (ref =1, 2,3)	0.87	0.24	-0.51	.610	0.50–1.51

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Any NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 163.38, LR chi2 (15) = 46.44, Prob>chi2: < .001

DCC and Severe NDI

The adjusted odds ratio for DCC and severe NDI was 0.64; 95% CI: 0.25–1.62, p = .348. The Hosmer- Lemeshow test indicated that there was no significant difference in the expected and observed frequencies of severe NDI outcome, suggesting that the final model was a good fit (p = .551)

Table 80. Adjusted odds ratio for severe NDI as a function of DCC at 36 months (n =268)

Severe NDI	**OR**	**Std. err.**	**Z**	P> | z |	95% CI
DCC (ref = ICC)	0.64	0.30	-0.94	.348	0.25–1.62
Maternal age	1.04	0.04	0.92	.356	0.96–1.12
PIH	3.13	1.83	1.94	.052	0.99–9.87

(ref = no PIH)					
Gestational Diabetes (ref = no gestational diabetes)	2.36	1.88	1.08	.281	0.50–11.22
Chorioamnionitis (ref = no chorioamnionitis)	1.24	0.60	0.45	.652	0.48–3.22
C-section (ref = vaginal delivery)	0.67	0.29	-0.92	.357	0.28–1.58
ANCS (ref = not received ANCS)	0.95	0.69	-0.07	.945	0.23–3.93
Multiple birth (ref = singleton pregnancy)	1.14	0.55	0.27	.788	0.44–2.93
Smoking (ref = no smoking while pregnant)	0.90	0.49	-0.19	.850	0.31–2.61
GA	0.95	0.14	-0.35	.726	0.71–1.27
Male (ref = female)	0.76	0.31	-0.68	.499	0.34–1.68
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	2.99	1.28	2.56	.010[a]	1.29–6.92
SGA (ref = no SGA)	0.26	0.29	-1.19	.233	0.03–2.35
Materially deprived (ref = 1,2,3)	1.88	0.80	1.50	.135	0.82–4.32
Socially deprived (ref =1, 2,3)	1.52	0.63	1.02	.306	0.68–3.40

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)

[a] Indicates statistical significance

Severe NDI adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = -89.23 LR chi2 (15) = 21.53, Prob>chi2: .121

DCC and cerebral palsy

The adjusted odds ratio for DCC and cerebral palsy was 1.12; 95% CI: 0.43–2.90, p = .813. The Hosmer-Lemeshow test yielded a p-value of .006, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 81. Adjusted odds ratio for cerebral palsy as a function of DCC at 36 months (n = 264)

Cerebral Palsy	OR	Std. err.	Z	P>|z|	95% CI
DCC (ref = ICC)	1.12	0.54	0.24	.813	0.43–2.90
Maternal age	1.01	0.05	0.29	.773	0.93–1.11
PIH (ref = no PIH)	1.43	0.94	0.55	.585	0.40–5.18
Gestational Diabetes (ref = no gestational diabetes)	1.92	1.50	0.83	.407	0.41–8.93
Chorioamnionitis (ref = no chorioamnionitis)	1.67	0.86	1.00	.316	0.61–4.57
C-section (ref = vaginal delivery)	0.97	0.45	-0.07	.942	0.39–2.40
ANCS (ref = not received ANCS)	0.75	0.54	-0.39	.694	0.18–3.11
Multiple birth (ref = singleton pregnancy)	1.06	0.52	0.12	.907	0.40–2.77
Smoking (ref = no smoking while pregnant)	1.33	0.75	0.50	.617	0.44–4.02
GA	0.87	0.14	-0.85	.394	0.63–1.20
Male (ref = female)	1.72	0.77	1.20	.228	0.71–4.15
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	3.48	1.59	2.73	.006[a]	1.42–8.51
SGA (ref = no SGA)	0.58	0.65	-0.48	.630	0.07–5.23
Materially deprived (ref = 1,2,3)	2.28	1.02	1.83	.067	0.94–5.50
Socially deprived (ref =1, 2,3)	0.72	0.32	-0.73	.468	0.30–1.74

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)

[a] Indicates statistical significance

Cerebral palsy adjusted for adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 78.90, LR chi2 (6) = 20.76, Prob>chi2: .145

DCC and cognitive delay

The adjusted odds ratio for DCC and cognitive delay was 3.38; 95% CI: 1.74–6.53, p =<.001. The Hosmer-Lemeshow test yielded a p-value of .028, indicating a statistically significant difference between observed and expected outcomes. This suggests that the logistic regression model does not fit the data well and its predicted probabilities may not be reliable.

Table 82. Adjusted odds ratio for cognitive delay as a function of DCC at 36 months (n = 253)

Cognitive delay	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	3.38	1.14	3.61	<.001	1.74–6.53
Maternal age	1.00	0.03	0.08	.934	0.95–1.06
PIH (ref = no PIH)	2.17	1.05	1.60	.110	0.84–5.62
Gestational Diabetes (ref = no gestational diabetes)	0.17	0.19	-1.60	.110	0.02–1.49
Chorioamnionitis (ref = no chorioamnionitis)	2.15	0.81	2.05	.040[a]	1.03–4.48
C-section (ref = vaginal delivery)	0.86	0.28	-0.47	.640	0.45–1.64
ANCS (ref = not received ANCS)	0.60	0.32	-0.94	.348	0.20–1.75
Multiple birth (ref = singleton pregnancy)	1.84	0.64	1.76	.079	0.93–3.64
Smoking (ref = no smoking while pregnant)	0.73	0.33	-0.71	.478	0.30–1.75
GA	0.88	0.10	-1.05	.292	0.70–1.11
Male (ref = female)	1.90	0.60	2.04	.041[a]	1.03–3.52
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	1.39	0.46	0.97	.331	0.72–2.67
SGA (ref = no SGA)	1.22	0.70	0.34	.731	0.40–3.74
Materially deprived (ref = 1,2,3)	2.76	0.87	3.23	.001[a]	1.49–5.11
Socially deprived (ref =1, 2,3)	0.84	0.26	-0.57	.570	0.45–1.55

ANCS: antenatal corticosteroid; C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Cognitive delay adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 137.59, LR chi2 (15) = 45.02, Prob>chi2: .001

DCC and hearing impairment

Model did not fit for hearing impairment due to small number of events.

DCC and visual impairment

The adjusted odds ratio for DCC and visual impairment was 0.39; 95% CI: 0.07–2.24, p = .289. The Hosmer- Lemeshow test indicated no significant difference between expected and observed frequencies of visual impairment outcome, suggesting that the final model was a good fit (.998).

Table 83. Adjusted odds ratio for visual impairment as a function of DCC at 36 months (n = 232)

Visual Impairment	**OR**	**Std. err.**	**Z**	P>|z|	95% CI
DCC (ref = ICC)	.39	0.35	-1.06	.289	0.07–2.24
Maternal age	1.02	0.07	0.23	.819	0.89–1.16
PIH (ref = no PIH)	2.04	1.98	0.73	.463	0.30–13.68
Gestational Diabetes (ref = no gestational diabetes)	3.25	3.84	1.00	.319	0.32–32.99
Chorioamnionitis (ref = no chorioamnionitis)	1.63	1.42	0.56	.577	0.29–8.99
C-section (ref = vaginal delivery)	1.08	0.80	0.11	.912	0.26–4.61
Multiple birth (ref = singleton pregnancy)	4.18	3.22	1.85	.064	0.92–18.95
Smoking (ref = no smoking while pregnant)	0.60	0.55	-0.55	.581	0.10–3.68
GA	0.66	0.15	-1.81	.070	0.42–1.03
Male	1.07	0.73	0.09	.926	0.28–4.10

(ref = female)					
Apgar score at 5 minutes <7 (ref = Apgar score at 5minutes≥7)	4.29	2.99	2.09	.037[a]	1.09–16.85
SGA (ref = no SGA)	2.78	2.91	0.98	.327	0.36–21.54
Materially deprived (ref = 1,2,3)	3.26	2.24	1.71	.086	0.84–12.56
Socially deprived (ref =1, 2,3)	1.25	0.80	0.35	.728	0.36–4.39

C-section: caesarean section; DCC: deferred cord clamping; GA: gestational age; PIH: pregnancy induced hypertension; SGA: small for gestational age (<10th percentile)
[a] Indicates statistical significance
Visual impairment adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)

Log likelihood = - 41.33, LR chi2 (14) = 23.10, Prob>chi2: .059

Propensity Score Matching:

To address baseline disparities between the exposed and unexposed cohorts, a propensity score matching (PSM) strategy was implemented to limit confounding and enhance comparability between groups. Exposed participants were matched with unexposed subjects who had similar likelihoods of receiving the exposure, based on their propensity scores, thereby allowing for a more unbiased estimation of the treatment effect. Propensity scores were calculated using a multivariable logistic regression model that included GA, male sex, C-section, and ANCS as covariates. Matching was conducted in Stata version BE 18.5 using a caliper width equal of 0.2 times the standard deviation of the logit-transformed propensity scores, with outliers outside this range excluded from the matched sample.

Table 84 demonstrated the Propensity score- matched odds ratio for neurodevelopmental outcomes at 18-24 months CA as a function of DCC.

Table 84. Propensity score- matched odds ratio at 18-24 months as a function of DCC

Outcomes	No. of matched pairs	Propensity Score-Matched OR	95% CI	P-value
Death/any NDI	116	1.09	0.98 – 1.21	.096
Death/severe NDI	104	0.98	0.89 – 1.08	.751
Any NDI	105	1.09	0.98 – 1.23	.106
Severe NDI	93	0.97	0.87 – 1.06	.518
Cerebral palsy	87	0.98	0.90 – 1.06	.651
Cognitive delay	87	0.92	0.81 – 1.02	.121
Motor delay	88	1.06	0.94 – 1.21	.304
Language delay	90	1.07	0.94 – 1.22	.295
Hearing Impairment	N/A	N/A	N/A	N/A
Visual Impairment	78	0.95	0.91 – 0.99	.045[a]

* Propensity score matched odds ratios adjusted for GA, male sex, C-section and ANCS
[a] Indicates statistical significance
ANCS: antenatal corticosteroid; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping
N/A= not applicable, due to lack of outcome in the DCC cohort

Table 84 presents the propensity score–matched odds ratios for neurodevelopmental outcomes at 18–24 months CA in relation to DCC. The results indicated that DCC was not significantly associated with death or any NDI, death or severe NDI, NDI alone, severe NDI, or any other individual outcome except visual impairment. Visual impairment was the only outcome that was significantly reduced in the DCC group after adjustment using propensity score matching (matched OR: 0.95, 95% CI: 0.91–0.99, p = .045).

Table 85 demonstrated the Propensity score- matched odds ratio for neurodevelopmental outcomes at 36 months CA as a function of DCC.

Table 85. Propensity score- matched odds ratio at 36 months as a function of DCC

Outcomes	No. of matched pairs	Propensity Score-Matched OR	95% CI	P-value
Death/any NDI	99	1.18	1.06 – 1.32	.003[a]
Death/severe NDI	95	1.01	0.91 – 1.11	.879
Any NDI	88	1.09	1.05 – 1.35	.004[a]
Severe NDI	84	0.99	0.91 – 1.07	.851
Cerebral palsy	101	0.97	0.89 – 1.04	.375
Cognitive delay	83	1.25	1.09 – 1.40	.001[a]
Hearing Impairment	N/A	N/A	N/A	N/A
Visual Impairment	93	0.98	0.93 – 1.03	.393

* Propensity score matched odds ratios adjusted for GA, male sex, C-section and ANCS
[a] Indicates statistical significance
ANCS: antenatal corticosteroid; DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping
N/A= not applicable, due to lack of outcome in the DCC cohort

Table 85 summarizes the propensity score–matched odds ratios for neurodevelopmental outcomes at 36 months CA in relation to DCC. The findings demonstrate that DCC was significantly associated with increased odds of death or any NDI (matched OR: 1.18, 95% CI: 1.06–1.32, p = .003), NDI alone (matched OR: 1.09, 95% CI: 1.05–1.35, p = .004), and cognitive impairment (matched OR: 1.25, 95% CI: 1.09–1.40, p = .001). However, these results may be influenced by the use of two different versions of cognitive assessment tools across two cohorts, and by different psychologists conducting the testing, which could introduce measurement bias and inter-rater variability, respectively.

Regression Analysis with Infants in the DCC Period

An additional regression analysis was conducted, focusing on infants from the DCC period (Period 2). In this analysis, the comparison group consisted of 134 infants who underwent ICC within the same interval. These ICC infants had been excluded from the primary analysis due to

discrepancies in the time frame of the original ICC cohort. Cognitive development at 36 months CA was assessed in both these DCC and ICC groups using the WPPSI-IV test. In contrast, cognitive outcomes for the primary ICC cohort at 36 months were assessed using WPPSI-III test.

The aim of this analysis was to examine whether differences in test structure, normative data, and scoring algorithms between the two WPPSI editions may influenced the observed associations. Such differences could have introduced measurement bias, led to misclassification, or attenuated true effects by altering the sensitivity and specificity for detecting cognitive delay. For the 18–24-month follow-up, identical standardized assessment tools were employed across both analyses.

Table 86. Maternal and neonatal baseline characteristics and short-term outcomes of infants in DCC period (N= 299)

Demographic Characteristics and short-term outcomes	**Infants had DCC (n= 165)**	**Infants had ICC (n= 134)**	**p -value***
Maternal age, years, median (IQR)	32 (28–37)	31 (27–35)	.059
Completed high school	112/128 (87.5)	106/114 (92.98)	.154
PIH	33/165 (20)	20/134 (14.93)	.253
Gestational diabetes	14/165 (8.48)	8/134 (5.97)	.408
Chorioamnionitis	36/165 (21.82)	26/134 (19.40)	.608
C-section	87/165 (52.73)	83/134 (61.94)	.110
ANCS	155/165 (93.94)	122/134 (91.04)	.340
Maternal antibiotics	116/165 (70.30)	83/133 (62.41)	.150
Multiparous	81/165 (49.09)	62/133 (46.62)	.671
Multiple Birth	45/165 (27.27)	46/134 (34.33)	.187
PROM	49/165 (29.70)	28/133 (21.05)	.090
Smoking	16/165 (9.70)	15/132 (11.36)	.641
Alcohol use	8/165 (4.85)	5/132 (3.79)	.657
Material deprivation Quintiles			

Quintile1 (most privileged)	27/158 (17.09)	15/128 (11.72)	.544
Quintile2	33/158 (20.88)	25/128 (19.53)	
Quintile3	30/158 (18.99)	32/128 (25)	
Quintile4	17/158 (10.76)	17/128 (13.28)	
Quintile5 (most deprived)	51/158 (32.28)	39/128 (30.47)	
Social deprivation Quintiles			
Quintile1 (most privileged)	27/158 (17.09)	15/128 (11.72)	
Quintile2	34/158 (21.52)	24/128 (18.75)	
Quintile3	32/158 (20.25)	18/128 (14.06)	.180
Quintile4	36/158 (22.79)	39/128 (30.47)	
Quintile5 (most deprived)	29/158 (18.35)	32/128 (25)	
GA in weeks, median (IQR)	27 (26–28)	26 (25–27)	.003[a]
Birth weight-grams, median (IQR)	900 (780–1050)	820 (640–1000)	.005[a]
Male	91/165 (55.15)	72/134 (53.73)	.806
SGA	18/165 (10.91)	18/134 (13.43)	.505
Apgar score at 5 minutes <7	49/165 (29.70)	53/134 (39.55)	.074
RDS	149/165 (90.30)	124/134 (92.54)	.495
BPD	85/160 (53.13)	87/133 (65.41)	.033[a]
PDA	95/165 (57.57)	88/134 (65.67)	.153
Surg. treated PDA	14/165 (8.48)	18/134 (13.43)	.169
Sepsis	19/165 (11.52)	22/134 (16.42)	.220
IVH	49/165 (29.70)	48/134 (35.82)	.261
Severe IVH	25/165 (15.15)	22/134 (16.42)	.765
PVL	4/165 (2.42)	9/134 (6.72)	.089
SNI	25/165 (15.15)	5/134 (3.73)	.001[a]
NEC	14/165 (8.48)	20/134 (14.92)	.081
ROP	117/153 (76.47)	105/124 (84.68)	.089
Severe ROP	11/153 (7.19)	18/124 (14.52)	.048[a]
Discharge home on oxygen	86/163 (52.76)	73/134 (54.48)	.768
Number of transfusions median (IQR)	0 (0–1)	0 (1–3)	< .001[a]
Total ventilation-days, median (IQR)	2 (1–12)	7 (1–22)	.001[a]
Total non-invasive resp. support-days median (IQR)	55 (40–60)	60 (42–65)	.085
Total suppl. oxygen-days	100	100	.008[a]

median (IQR)	(80–100)	(80–140)	
NICU stay-days, median (IQR)	90 (80–110)	100 (90–120)	.001[a]

* Mann-Whitney U test for continuous variables which are not normally distributed, Chi-squared test for categorical variables and Fisher's exact test when the cell count <5

[a] Indicates statistical significance ($p < .05$)

Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise

The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroid; BPD: bronchopulmonary dysplasia; C-section: caesarean section, DCC: deferred cord clamping; GA: gestational age; ICC: immediate cord clamping; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the membrane; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SGA: small for gestational age (<10th percentile); SNI: severe neurological injury

Infants in the DCC group were delivered at later gestational ages, had greater birth weights and increased proportion of SNI. Conversely, infants in the ICC group demonstrated a higher incidence of BPD, severe ROP and required prolonged mechanical ventilation.

At 18–24 months, 153 children (12 lost to follow-up) from the DCC cohort and 118 from the ICC cohort (16 lost to follow-up) were included in the analysis. The estimated associations were consistent across both analysis periods with the exception of motor delay, for which the association reached statistical significance after propensity score matching.

Tables 87 presents the crude, adjusted and propensity matched odds ratios comparing DCC and neurodevelopmental outcomes at 18-24 months corrected age.

Table 87. Odds ratios for Neurodevelopmental Outcomes in the DCC Period Infants: DCC vs. ICC Group at 18- 24 months (N= 271)

Outcomes	**DCC (n = 153)**	**ICC (n = 118)**	**p-value**	**Crude OR (95% CI)**	**Adjusted OR[*] (95% CI)**	**Propensity Score-matched OR[‡] (95% CI)**
Death/Any NDI, n (%)	76/116 (65.52)	50/84 (59.52)	.386	1.29 (0.69 – 2.40)	1.08 (0.54 – 2.16)	1.02 (0.84 – 1.21)
Death/Severe NDI, n (%)	27/104 (25.96)	20/76 (26.32)	.988	0.99 (0.48 – 2.07)	1.06 (0.53 – 2.15)	1.02 (0.87 – 1.18)
Any NDI, n (%)	65/105 (61.90)	45/79 (56.96)	.499	1.23 (0.65 – 2.32)	1.09 (0.53 – 2.26)	1.02 (0.83 – 1.22)

Severe NDI, n (%)	16/93 (17.20)	15/71 (21.13)	.525	0.78 (0.33 – 1.84)	0.80 (0.35 – 1.86)	0.98 (0.84 – 1.14)
Cerebral Palsy, n (%)	10/87 (11.49)	8/73 (10.96)	.915	1.06 (0.35 – 3.27)	1.37 (0.43 – 4.44)	1.03 (0.90 – 1.17)
Cognitive delay, n (%)	18/87 (20.69)	21/76 (27.63)	.300	0.68 (0.31 – 1.50)	0.58 (0.23 – 1.48)	0.96 (0.83 – 1.09)
Motor delay, n (%)	34/88 (38.64)	24/69 (34.78)	.619	1.18 (0.58 – 2.40)	1.77 (0.73 – 4.27)	1.20[a] (1.02 – 1.39)
Language delay, n (%)	43/90 (47.78)	31/71 (43.66)	.603	1.18 (0.60 – 2.31)	1.26 (0.60 – 2.63)	1.18 (0.86 – 1.25)
Hearing Impairment, n (%)	0/77 (0)	1/66 (1.52)	.278	N/A	N/A	N/A
Visual Impairment, n (%)	1/78 (1.28)	10/74 (13.51)	.004	0.08[a] (0.002 – 0.62)	0.11 (0.01 – 1.07)	0.89[a] (0.82 – 0.96)

*Adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)
‡Propensity score matched odds ratios adjusted for GA, male sex, C-section and ANCS
[a] Indicates statistical significance ($p<0.05$)
Data are expressed as n/N (%) unless specified otherwise
The variables have different denominators because not all variables had all data available
N/A= not applicable, due to lack of outcome in the DCC cohort

For 36 months, data were available for 145 children from the DCC cohort (8 lost to follow-up) and 108 from the ICC cohort (10 lost to follow-up).

Tables 88 provide a comparative analysis of baseline maternal and neonatal characteristics, as well as short-term neonatal morbidities of infants between two groups available for 36 months evaluation.

Table 88. Maternal and neonatal baseline characteristics and short-term outcomes of infants in DCC period Infants for 36 months Follow-up (N= 253)

Demographic Characteristics and short-term outcomes	**Infants had DCC (n= 145)**	**Infants had ICC (n= 108)**	**p -value***
Maternal age in years, median (IQR)	33 (28–47)	32 (27–45))	.132
Completed high school	103/117 (88.03)	90/96 (93.75)	.155
PIH	30/145 (20.69)	19/108 (17.59)	.538
Gestational diabetes	11/145 (7.59)	5/108 (4.63)	.339

Chorioamnionitis	29/145 (20)	21/108 (19.44)	.913
C-section	76/145 (52.41)	66/108 (61.11)	.168
ANCS	136/145 (93.79)	98/108 (90.74)	.362
Maternal antibiotics	95/134 (70.90)	61/102 (59.80)	.075
Multiparous	69/134 (51.49)	51/102 (50)	.820
Multiple Birth	39/145 (26.90)	34/108 (31.48)	.426
PROM	40/134 (29.85)	22/102 (21.57)	.152
Smoking	12/145 (8.28)	11/107 (10.28)	.585
Alcohol use	8/134 (5.97)	4/102 (3.92)	.478
Material deprivation Quintiles			
Quintile1 (most privileged)	24/138 (17.39)	13/102 (12.75)	
Quintile2	27/138 (19.57)	20/102 (19.60)	
Quintile3	29/138 (21.01)	26/102 (25.49)	.841
Quintile4	16/138 (11.59)	13/102 (12.75)	
Quintile5 (most deprived)	42/138 (30.44)	30/102 (29.41)	
Social deprivation Quintiles			
Quintile1 (most privileged)	24/138 (17.39)	14/102 (13.73)	
Quintile2	31/138 (22.46)	22/102 (21.57)	
Quintile3	28/138 (20.30)	13/102 (12.74)	.318
Quintile4	31/138 (22.46)	27/102 (26.47)	
Quintile5 (most deprived)	24/138 (17.39)	26/102 (25.49)	
GA in weeks, median (IQR)	27 (26–28))	26 (24–27))	.001[a]
Birth weight-grams, median (IQR)	900 (750–1100)	820 (620–1000)	.004[a]
Male	79/145 (54.48)	58/108 (53.70)	.902
SGA	16/145 (11.03)	16/108 (14.81)	.371
Apgar score at 5 minutes <7	44/145 (30.34)	45/108 (41.67)	.062
RDS	131/145 (90.34)	100/108 (92.59)	.530
BPD	75/141 (53.19)	72/107 (67.29)	.025[a]
PDA	82/145 (56.55)	73/108 (67.59)	.075
Surg. treated PDA	10/145 (6.90)	13/108 (12.04)	.159
Sepsis	16/145 (11.03)	18/108 (16.67)	.194
IVH	47/145 (32.41)	39/108 (36.11)	.539
Severe IVH	25/145 (17.24)	19/108 (17.59)	.942
PVL	4/145 (2.76)	7/108 (6.48)	.213

SNI	25/145 (17.24)	1/108 (0.93)	<.001[a]
NEC	11/145 (7.59)	18/108 (16.67)	.025[a]
ROP	101/134 (75.37)	82/98 (83.67)	.126
Severe ROP	11/134 (8.21)	17/98 (17.35)	.035[a]
Discharge home on oxygen	73/143 (51.05)	59/108 (54.63)	.574
Number of transfusions median (IQR)	0 (0–1)	1 (0–3)	<.001[a]
Total ventilation-days median (IQR)	3 (2–12)	12 (2–25)	.001[a]
Total non-invasive resp. support-days median (IQR)	50 (40–70)	50 (42–72)	.056
Total suppl. oxygen-days median (IQR)	90 (60–130)	100 (50–150)	.002[a]
NICU stay-days median (IQR)	90 (70–110)	100 (80–130)	.001[a]

* Mann-Whitney U test for continuous variables which are not normally distributed, Chi-squared test for categorical variables and Fisher's exact test when the cell count <5

[a] Indicates statistical significance ($p < .05$)

Data for categorical variables are expressed as n/N (%) and for continuous variables are expressed as median (IQR)unless specified otherwise

The variables have different denominators because not all variables had all data available

ANCS: antenatal corticosteroid; BPD: bronchopulmonary dysplasia; C-section: caesarean section; DCC: deferred cord clamping; GA; gestational age; ICC: immediate cord clamping; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PDA: patent ductus arteriosus; PIH: pregnancy induced hypertension; PROM: prolonged rupture of the membrane; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SGA: small for gestational age (<10th percentile); SNI: severe neurological injury

Infants exposed to DCC tended to be born at slightly more advanced gestational ages and with correspondingly higher birth weights.

Tables 89 presents the crude, adjusted and propensity matched odds ratios comparing DCC and neurodevelopmental outcomes at 36 months corrected age. The estimated associations for outcomes such as death or any NDI, isolated NDI and cognitive delay varied substantially in both direction and magnitude, compared to previous findings. Notably, the association between DCC and a decreased risk of visual impairment was statistically significant. This divergence may reflect the impact of using different cognitive assessment tests, WPPSI-III vs WPPSI-IV, which potentially influenced the observed outcomes.

Table 89. Odds ratios for Neurodevelopmental Outcomes in the DCC Period Infants: DCC vs. ICC Group at 36 months (N= 253)

Outcomes	DCC (n = 145)	ICC (n = 108)	p-value	Crude OR (95% CI)	Adjusted OR* (95% CI)	Propensity Score-matched OR‡ (95% CI)
Death/Any NDI	53/99 (48.31)	51/74 (66.67)	.041[a]	0.52 (0.23–1.02)	0.51 (0.23–1.14)	0.77[a] (0.64–0.90)
Death/Severe NDI	19/95 (20)	14/70 (20)	1	1 (0.43–2.35)	1.09 (0.41–2.91)	0.98 (0.82–1.15)
Any NDI	42/88 (47.73)	46/69 (66.67)	.018[a]	0.46[a] (0.23–0.92)	0.44 (0.19–1.00)	0.73[a] (0.60–0.86)
Severe NDI	8/84 (9.52)	9/65 (13.85)	.411	0.65 (0.21–2.05)	0.65 (0.18–2.37)	1.01 (0.93–1.09)
CP	9/101 (8.91)	9/62 (14.52)	.268	0.58 (0.19–1.76)	1.25 (0.30–5.27)	N/A£
Cognitive delay	37/83 (44.58)	36/63 (57.14)	.133	0.60 (0.30–1.23)	0.68 (0.30–1.53)	0.77[a] (0.61–0.93)
Hearing impairment	0/91	1/50 (2)	.176	N/A	N/A	N/A
Visual impairment	3/93 (3.23)	11/64 (17.19)	.003[a]	0.16[a] (0.03–0.65)	0.12[a] (0.02–0.71)	N/A£

*Adjusted for maternal age, PIH, gestational diabetes, chorioamnionitis, C-section, ANCS, multiple birth, smoking, GA, male, Apgar score at 5 min <7, SGA, material deprivation (ref=1,2,3) and social deprivation (ref=1,2,3)
‡Propensity score matched odds ratios adjusted for GA, male sex, C-section and ANCS
[a] Indicates statistical significance ($p<0.05$)
Data are expressed as n/N (%) unless specified otherwise
The variables have different denominators because not all variables had all data available
N/A= not applicable, due to lack of outcome in the DCC cohort.
N/A£= not applicable, propensity score matching is not feasible as no suitable matches were found within the specified caliper of 0.2 between treatment and control groups

CHAPTER FOUR: DISCUSSION

Summary of Results:

A comparative analysis was conducted between cohorts undergoing deferred cord clamping (DCC) and immediate cord clamping (ICC), using two datasets with follow-up evaluations at 18-24 months and 36 months corrected age. The study population comprised preterm infants born at <29 weeks' gestation at Foothills Medical Centre (FMC) who required admission to the regional Neonatal Intensive Care Unit (NICU) between 1 January 2006 and 31 December 2017. The 18–24-month analytical sample included 153 preterm infants in the DCC group and 414 in the ICC group with available outcome data. The 36- month dataset consisted of 134 preterm infants in the DCC group with available follow-up data, and 11 deaths (0 deaths at 36 months and 11 deaths between 18 and 24 months). In comparison, the ICC cohort included 346 infants with follow-up data and 30 deaths (1 at 36 months and 29 between 18 and 24 months).

The findings indicated that DCC was not significantly associated with death or any neurodevelopmental impairment (NDI) at 18–24 months of corrected age. In contrast, the 36-month analysis demonstrated significant associations between DCC and death or any NDI, any NDI alone, and cognitive delay. These elevated associations may, in part, reflect the use of different versions of the cognitive assessment tool– the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)– at 36 months, as well as different psychologists conducting the testing. Specifically, the ICC cohort was evaluated using the WPPSI-III, while the DCC cohort was assessed using the WPPSI-IV. It is noteworthy that the 18–24-month assessments employed the same instrument, the Bayley Scales of Infant Development, Third Edition (BSID-III), across both cohorts.

Neurodevelopmental Outcomes

Neurodevelopmental Outcomes at 18-24 months

A total of 527 children, representing 93.11% of the overall cohort (527 out of 566 children eligible for follow-up) completed neurodevelopmental evaluation at 18-24 months corrected age. Follow-up rates were comparable between the DCC and ICC groups (92.21% vs. 93.45%), with no statistically significant difference (p = .806)

The proportion of infants experiencing death or any NDI was slightly higher in the DCC cohort than in the ICC cohort (65.52% vs. 59.83%). Nonetheless, after applying propensity score matching, this difference was not statistically significant (matched odds ratio, OR: 1.09, 95% CI: 0.98–1.21, p = .096), with adjustments made for gestational age at birth (GA), caesarean section (C-section), antenatal corticosteroid use (ANCS) and male sex.

The rate of death or severe NDI was lower in the DCC group than in the ICC group (25.96% vs 29.25%). This difference was not statistically significant after propensity score matching; (matched OR: 0.98, 95% CI: 0.69–1.08, p = .751).

A statistically significant difference was observed in the incidence of hearing impairment between the DCC and ICC groups, with no cases reported in the DCC group compared to the ICC group (0% vs 7.80%; p = .012).

Children exposed to DCC had a lower rate of visual impairment than those exposed to ICC (1.28% vs 7.11%). This difference was statistically significant after propensity score matching, (matched OR: 0.95, 95% CI: 0.91–0.99, p = .045).

Neurodevelopmental Outcomes at 36 months

Of the total cohort, 480 children, representing 91.25% of the overall cohort (480 out of 526 children eligible for follow-up) completed neurodevelopmental evaluation at 36 months corrected age. Follow-up rates were comparable between the DCC and ICC groups (94.37% vs 90.10%), with no statistically significant difference observed (p= .256).

Children in the DCC cohort showed a higher rate of death or any NDI compared with those who received ICC (53.54% vs. 38.55%). This relationship remained significant following propensity score matching (matched OR: 1.18, 95% CI: 1.06–1.32, p = .003), after adjusting for GA, C-section, ANCS, and male sex.

Children who received DCC demonstrated a slightly lower incidence of death or severe NDI than those who underwent ICC (20.00% vs. 20.68%). However, this difference was not statistically significant after propensity score matching, (matched OR: 1.01, 95% CI: 0.91–1.11, p = .879).

The prevalence of cognitive delay was markedly greater among children in the DCC cohort compared with those in the ICC cohort (44.58% vs. 23.79%, p < .001). This association remained significant after propensity score matching (matched OR: 1.25, 95% CI: 1.09–1.40, p = .001).

A significant difference in the proportion of hearing impairment was observed between the DCC and ICC groups, with no cases reported in the DCC group compared with 6.15% in the ICC group (p = .015). An odds ratio could not be calculated because no hearing impairment occurred in the DCC group.

Additional Analyses: Regression Models Limited to the DCC Time-Period Cohort

An additional regression analysis was performed, focusing specifically on infants from the DCC period (**period 2**). The comparison group comprised 134 infants who received ICC during the same interval. Cognitive outcomes at 36 months CA were assessed in both cohorts using the WPPSI-IV. This analysis aimed to investigate whether differences in test structure, normative data, and scoring algorithms between the WPPSI-III and WPPSI-IV may have influenced the previously observed associations. The estimated associations at 36-month—including death or any NDI (matched OR: 0.77, 95% CI: 0.64–0.90), isolated NDI (matched OR: 0.73, 95% CI: 0.60–0.86), and cognitive delay (matched OR: 0.77, 95% CI: 0.61–0.93)—varied substantially in both direction and magnitude compared with earlier findings. This variation may reflect the impact of using different cognitive assessment instruments (WPPSI-III versus WPPSI-IV), which could have affected the observed outcomes. However, the associations were generally consistent with the 18–24-month results of the previous analysis, with the exception that motor delay reached significance in this cohort (matched OR: 1.20, 95% CI: 1.02–1.39).

Comparison with Previous Studies

Comparison of Neurodevelopmental Outcomes

For 18-24 months follow-up

In our cohort study, DCC demonstrated no significant associations between death or any NDI, death or severe NDI, any NDI alone, severe NDI, cerebral palsy, cognitive, motor, language scores at 18–24 months follow-up but showed significant lower odds visual impairment. No occurrences of hearing impairment were also detected within the DCC group. It is important to note that neurodevelopmental outcomes are inconsistently reported across studies comparing

DCC and ICC in preterm infants. While some studies support our findings (23, 122, 175), others report conflicting results, reflecting heterogeneity in the literature.

Our finding regarding the absence of a significant association between DCC and severe NDI, aligns with the multicentre, randomised Australian Placental Transfusion Study (APTS trial) conducted by Robledo et al. (175) which included 665 preterm infants born before 30 weeks' gestation across 25 centres in seven countries. That study similarly reported no significant association between DCC and severe NDI at 2 years CA (risk ratio, RR: 0.88, 95% CI: 0.74–1.04), although a significant reduction was observed in the composite outcome of death or severe NDI among infants who received DCC (RR: 0.83, 95% CI: 0.72 – 0.95)). Individual components of the neurodevelopmental outcomes were not separately reported.

A retrospective cohort study by Handley et al. (122) also found no significant association between DCC and severe NDI (adjusted OR: 0.74, 95% CI: 0.52–1.05)., cerebral palsy (adjusted OR: 1.01, 95% CI: 0.73–1.40) or delays in cognitive (adjusted OR: 0.88, 95% CI: 0.68–1.18), motor or language development at 18-24 months. In contrast, that study did report a significantly lower odds of death or severe NDI among infants who received DCC (adjusted OR: 0.64, (95% CI: 0.50–0.83). No association was found with hearing impairment (adjusted OR: 0.91, 95% CI: 0.44–1.88). Visual impairment or the combined outcome of death or any NDI were not assessed.

Another randomized control trial (RCT) by Armstrong- Buisseret et al. (23) reported findings similar to ours, showing no significant association between DCC and any adverse neurodevelopmental outcomes – defined as moderate or severe impairment in at least one of five domains: motor, cognitive, language, hearing or vision (RR: 0.75, 95% CI: 0.41–1.39). However, a significant reduction was observed in the composite outcome of death or adverse

neurodevelopmental outcome among infants who received deferred cord clamping (RR: 0.61, 95% CI: 0.39–0.96). Other individual neurodevelopmental outcomes were not reported in that trial.

The APTS (177), also reported findings contrasting with ours, showing a significant reduction in the risk of death or major disability–defined as cerebral palsy, severe visual impairment, hearing loss requiring assistive devices, major language or speech difficulties, or cognitive delay, at two years CA (RR: 0.83, 95% CI: 0.72–0.95, p = 0.01). DCC for at least 60 seconds was associated with a 17% relative reduction in the risk of death or disability, and a 30% reduction in mortality.

For 36 months follow-up

In contrast to the findings at the 18–24 months follow-up, assessment at 36 months CA revealed a significant association between exposure to DCC and higher odds of the composite outcome of death or any NDI as well as any NDI alone and cognitive delay. It is important to note that these results may have been affected using different editions of the WPPSI—either the fourth (WPPSI-IV) or third (WPPSI-III) edition—for cognitive assessments across the DCC and ICC cohorts. As no studies have directly compared the psychometric properties of WPPSI-IV and WPPSI-III in clinical populations, further research is warranted to determine whether variations between editions influenced the observed outcomes. Consistent with earlier findings, the DCC group continued to show no cases of hearing impairment at 36 months.

However, in the supplementary analysis restricted to infants from the DCC period—where cognitive outcomes were assessed using the same WPPSI-IV instrument—the observed associations differed markedly in both direction and magnitude from the primary findings. Following propensity score matching, DCC was associated with a trend toward lower odds of

death or any NDI, NDI alone, and cognitive impairment. This discrepancy may be attributable to the use of different cognitive assessment tools (WPPSI-III versus WPPSI-IV) in the earlier analyses, which could have influenced the observed outcomes.

An RCT, conducted by Berg et al. (125) among term infants, assessed neurodevelopmental outcomes at 3 years using the Ages and Stages Questionnaire (ASQ). Their findings contrast with ours, as no statistically significant differences were observed between the DCC and ICC groups across any ASQ domains.

We speculate that the possible underlying mechanisms for the benefits of DCC include the following: DCC allows additional blood to flow from the placenta to the infant, improving cardiac output and systemic perfusion, including cerebral blood flow. Better cerebral perfusion reduces the risk of intraventricular haemorrhage (IVH), a major cause of neurodevelopmental impairment in preterm infants. Increased iron sores reduce the risk of iron deficiency anaemia during infancy. Iron is critical for myelination, neurotransmitter synthesis, and energy metabolism in the developing brain. DCC also supports a smother transition from fetal to neonatal circulation, reducing fluctuations in blood pressure and preventing brain injury. It lowers the risk of hypoperfusion or hyperperfusion, both of which can contribute to brain injury. Fewer complications, such as stable blood pressure, and a lower risk of infections indirectly support better neurodevelopment. Increased haemoglobin improves oxygen-carrying capacity, preventing hypoxic-ischaemic injury, which is linked to poor cognitive outcomes. Documented benefits of DCC include lower rates of IVH and necrotising enterocolitis, improved motor and cognitive scores at 18–24 months, and better long-term neurodevelopmental outcomes in some cohorts.

At present, evidence on neurodevelopmental outcomes at 36 months CA among preterm infants exposed to DCC remains limited. To our knowledge, no prior studies have conducted a comprehensive evaluation of long-term neurodevelopment at this age using standardised, in-person assessments while simultaneously accounting for a wide range of maternal and neonatal variables, and early postnatal morbidities. The present study contributes meaningfully to the literature by providing a detailed and methodologically robust analysis of the potential impact of DCC on long-term neurodevelopment. The inclusion of extensive baseline and clinical covariates, combined with propensity-score matching to reduce confounding, strengthens the internal validity of our findings. In doing so, this study offers novel insights into an aspect of neonatal research that remains comparatively under-explored.

Growth

No evidence of poor growth was observed, as none of the three growth parameters- weight, height and head circumference fell below -2 z scores at both 18-24- and 36-months of follow-up. Additionally, there were no statistically significant differences in these measures between the DCC and ICC groups within either the small for gestational age (SGA) or appropriate for gestational age (AGA) categories.

In our study, DCC was associated with improved height and head circumference in SGA and AGA children at the18–24-months follow-up. This positive trend persisted in the SGA group at 36 months. However, among AGA children, growth parameters were lower in those who received DCC compared with those who underwent immediate cord clamping. SGA infants are often affected by placental insufficiency and diminished iron stores at birth (178). The benefits observed in this group may be attributed to the physiological advantages conferred by deferred cord clamping. Deferred cord clamping increases blood volume, enhances perfusion to vital

organs, raises iron levels and facilitates the transfer of stem cells (179). These effects may reduce the need for transfusions and are associated with lower rates of complications such as BPD, NEC, and sepsis. Collectively, these findings suggest that DCC may be particularly beneficial for SGA infants, who are at increased risk of postnatal growth failure and developmental delay.

Comparison of Short-Term Outcomes

Patent Ductus Arteriosus (PDA): This is a common complication in preterm infants. In the present study, the overall incidence of PDA including cases requiring surgical ligation was lower in the DCC cohort than in the ICC cohort. This reduction may reflect the physiological benefits of DCC, such as improved cardiovascular stability, preserved blood flow and reduced need for blood transfusion, all of which promote early ductal closure. Previous studies have demonstrated a four-fold higher likelihood of PDA requiring medical or surgical intervention among infants who received blood transfusions compared with those who did not (80), supporting the observed reduction in surgically treated PDA in the DCC group. These findings are align with an RCT by Mordi et al., which reported a lower rate of PDA requiring treatment in infants born at <33 weeks' gestation who received DCC (32.0%) compared with those who received ICC (33.5%), although this difference was not statistically significant (180).

Retinopathy of Prematurity (ROP): This is a complex vasoproliferative retinal disorder influenced by factors, such as lower GA, low birth weight and prolonged exposure to supplemental oxygen. In the present study DCC was associated with significantly lower odds of severe ROP in preterm infants compared with immediate cord clamping. This association may relate to the shorter duration of oxygen support, and the smaller proportion of infants discharged home on supplemental oxygen in the DCC group. This finding is partially supported by Mordi et al. who reported a lower incidence and reduced risk of severe ROP in the DCC group among

infants born at <30 weeks' gestation; however, this association did not reach statistical significance (risk ratio, RR: 0.75, 95% CI: 0.50–1.11) (180).

Sepsis: Sepsis remains a major cause of morbidity and mortality in preterm infants, largely owing to their immature immune systems. In this study, DCC was associated with a significantly reduced risk of sepsis. This protective effect may be due to the transfer of immune-supportive cells (such as haematopoietic stem cells, neutrophils, and monocytes), improved haemoglobin and iron stores, and a reduced need for early blood transfusion following deferred cord clamping. This finding is supported by Lodha et al., who reported significantly lower odds of late onset sepsis among preterm infants (22–28 weeks' gestation) who received deferred cord clamping (propensity-score matched OR: 0.81, 95% CI: 0.69–0.95) (92).

Blood Transfusion: Preterm infants who received DCC required significantly fewer blood transfusions than those who underwent immediate cord clamping. This may result from the additional placental blood volume transferred to the infant while the umbilical cord remained intact. This outcome aligns with findings by Brown et al., who reported that DCC lasting for ≥30 seconds in preterm infants born at <33 weeks' gestation, significantly reduced the odds of requiring blood transfusion compared with immediate cord clamping (OR: 0.60, 95% CI: 0.47–0.77) (179).

Intraventricular Haemorrhage (IVH): In this study, exposure to DCC compared with ICC, was associated with higher odds of severe IVH, (adjusted OR: 1.97, 95% CI:1.09– 3.55) despite no significant difference in the incidence of any grade IVH (adjusted OR:1.34, 95% CI: 0.86–2.09). The increased incidence of severe IVH in preterm infants is largely attributed to the fragility of the germinal matrix vasculature, immature cerebral autoregulation and

haemodynamic instability. Intraventricular haemorrhage remains a major concern in preterm birth, affecting approximately 25% of infants born before 30 weeks' gestation. Although DCC is generally linked to improved haematologic status and circulatory stability, inclusion of highly vulnerable infants born before 29 weeks GA in our cohort may have contributed to the elevated risk of severe IVH observed. Contrasting results were reported by Hemmati et al. who studied infants born between 26–34 weeks' gestation; while the incidence of IVH of any grade was similar between groups, severe IVH was significantly lower in the DCC group than in the ICC group (1.4% vs 10.1%; p = .036) (22).

No significant differences were found between the DCC and ICC groups regarding respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), IVH, periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), or the duration of mechanical ventilation. The more favourable perinatal profile in the DCC group including higher GA at birth, lower transfusion rates, shorter oxygen supplementation, and fewer infants discharged home on oxygen–may partly explain these comparable outcomes. Similar results have been reported by Chiruvolu et al., Nevill et al., Rabe et al. and Wang et al. in studies involving preterm infants (181-184).

Impact of Bias on the Results

As with all retrospective cohort studies, this study was susceptible to various forms of bias. Selection and information biases are inherent risks in cohort designs; however, extensive measures were implemented to minimise these biases throughout the study.

Selection bias may have arisen during cohort formation. To mitigate this risk, inclusion and exclusion criteria were explicitly defined during the study design phase to ensure consistent and

systematic participant selection. In addition, the presence of infants who received ICC during the DCC implementation period—particularly those expected to have poorer neurodevelopmental outcomes—had the potential to bias the findings in favour of DCC by disproportionately inflating adverse outcomes within the ICC group. To minimise this source of bias, these cases were excluded from the primary analysis. These steps were undertaken to enhance the internal validity of the study and to ensure that the comparison between exposure groups reflected true differences rather than artefacts of cohort misclassification.

Information bias may have occurred due to the use of two different editions of the WPPSI to evaluate cognitive outcomes in the DCC and ICC cohorts. To mitigate this issue, an additional regression analysis was conducted within the DCC implementation period, during which both DCC and ICC infants were assessed using the WPPSI-IV. This approach enabled an evaluation of the extent to which discrepancies between WPPSI editions may have influenced the observed associations. Furthermore, operational definitions for NDI, severe NDI, cerebral palsy, and cognitive, motor, and language delay, as well as hearing and visual impairment, were explicitly established at the study design stage to reduce the likelihood of misclassification bias.

The study relied on routinely collected clinical data, assuming the accuracy and completeness of entries within institutional databases. However, documentation within NICU discharge summaries and neurodevelopmental follow-up assessments could not be independently validated, introducing the potential for recording or reporting inaccuracies. Such limitations are inherent in retrospective cohort designs and may contribute to residual information bias despite efforts to standardise outcome definitions and assessment procedures.

Attrition bias was unlikely to have materially influenced the findings, as follow-up rates among surviving infants were high—93.11% at 18–24 months and 91.25% at 36 months—and comparable between the DCC and ICC groups.

Notably, the higher proportion of mothers from materially deprived backgrounds and the increased prevalence of SGA infants within the DCC cohort may have independently contributed to both short-term morbidities and long-term neurodevelopmental impairments, irrespective of the cord-clamping intervention (185-187). Furthermore, variations between infants who were followed up and those lost to follow-up may have introduced unmeasured confounding and selection bias. For instance, the DCC cohort evaluated at 36 months included mothers with significantly lower rates of chorioamnionitis and fewer infants requiring surgical ligation for PDA (188, 189). In contrast, the ICC cohort assessed at 36 months showed a higher rates of multiple births, male sex, and RDS—all recognised risk factors for long-term neurodevelopmental delay (190, 191). To further assess the potential impact of loss to follow-up, a sensitivity analysis was conducted comparing baseline characteristics of infants who completed follow-up with those who were lost to follow-up. Any observed differences were subsequently accounted for through logistic regression and propensity score methods, thereby reducing the risk that differential attrition introduced systematic bias. These analytical steps increased confidence that the estimated associations reflect true effects rather than artefacts arising from incomplete follow-up.

Implications on Clinical practice:

This study provided a comprehensive evaluation of neurodevelopmental and clinical outcomes at 18–24 months and 36 months CA through standardised, in-person assessments, while accounting

for a wide range of maternal, neonatal, and early postnatal factors. By examining the effects of DCC within a well-defined preterm population in the NICU at FMC, the study contributes meaningful evidence regarding both short-term morbidities and longer-term developmental trajectories. The findings carry important clinical and policy implications. The observed associations between DCC and lower rates of several major neonatal morbidities—including PDA ligation, sepsis, severe ROP, blood transfusion requirements, and oxygen supplementation—underscore the potential of DCC to improve early outcomes in preterm infants.

Although higher odds of death or any NDI and cognitive delay at 36 months were observed in the DCC group, these associations are likely influenced by baseline differences between cohorts, variability in DCC implementation, differing resuscitation needs, and the use of different editions of cognitive assessment tools across follow-up periods. When analyses were restricted to cohorts assessed exclusively with the same cognitive instrument, DCC was associated with lower odds of death or any NDI and cognitive delay, reinforcing the importance of consistent measurement methods in outcome evaluation.

The study findings do not challenge existing clinical practice; rather, they highlight the need for future multicentre, prospective, or randomised studies with larger sample sizes and harmonized long-term follow-up methodologies to more accurately delineate the true impact of DCC. The results support the continued and expanded adoption of DCC in routine care for preterm deliveries and may inform future revisions of national and international perinatal guidelines. By integrating an extensive set of maternal, neonatal, and postnatal variables, this study establishes a robust framework for subsequent research, supports the generation of new hypotheses and reinforces the importance of individualised, evidence-based approaches in neonatal care.

Strengths

The study has several strengths:

- Comprehensive, multidisciplinary follow-up, conducted by trained specialists at the neonatal follow-up clinic. The follow-up rates were exceptionally high, 93.11% at 18–24 months and 91.25% at 36 months corrected age. Fewtrell et al. suggested that follow-up rates exceeding 80% are adequate for studies evaluating long-term neurodevelopmental outcomes (192), thereby supporting the robustness and reliability of the data presented.
- All data were derived from standard clinical practice, enhancing the external validity and applicability of findings to real-world neonatal care settings.
- Neurodevelopmental assessment at 36 months CA allowed for more accurate diagnosis, particularly of cognitive outcomes, which are less reliably predicted by evaluations conducted before 24 months of age (193-195).
- Several strategies were implemented to reduce bias and confounding during both design and analysis phases. The use of a priori operational definitions ensured consistency and minimised measurement bias.
- To our knowledge, this is the first study to report detailed neurodevelopmental outcomes in preterm infants at 36 months CA using standardised, in-person assessments, thereby addressing a major gap in existing literature.

Limitations

Despite the strengths of this study, several limitations warrant consideration. These limitations are outlined to provide transparency and contextualise the study's findings.

- **Study Design Limitations:**
    - The retrospective design introduces inherent methodological constraints, including potential selection bias and residual confounding, due to the absence of blinding and randomisation.
    - A subset of infants was excluded because they received ICC within the intended DCC window. As these infants were of lower gestational age and experienced higher rates of BPD and prolonged mechanical ventilation, their exclusion may have contributed to selection bias.
- **Population – Specific Limitations**
    - Infants who received DCC were more likely to be associated with planned deliveries, evidenced by higher GA at birth and greater administration of ANCS. They also had more stable perinatal courses, reflected in lower transfusion needs, fewer days of ventilation and oxygen support, and a smaller proportion requiring oxygen at discharge. Such factors may confound the interpretation of DCC-related outcomes.
- **Measurement and Analysis Limitations**
    - Precise data on the actual duration of DCC were unavailable, potentially introducing misclassification bias.
    - Neurodevelopmental outcomes were obtained from a single institution where differences in assessment tools and attrition rates, may have limited comparability and generalisability to the wider population of preterm infants in other neonatal centers across Canada.
    - The relatively small sample size for individual neurodevelopmental outcomes, may have limited statistical power to detect potential differences between groups.

- Conducting multiple statistical analyses across several outcomes increases the likelihood of type I error due to multiplicity.
- The Hosmer–Lemeshow goodness-of-fit test indicated that some logistic regression models did not fit the data adequately, suggesting discrepancies between predicted probabilities and actual outcomes. This may reduce the reliability of those models. Possible explanations include limited sample size, numerous unique covariate profiles, unmeasured confounders, or underlying nonlinear relationships not captured by the model. Nonetheless, other models demonstrated acceptable fit. Although logistic regression remains an established method for binary outcomes, future studies could consider alternative modelling approaches or incorporate additional relevant predictors to improve model performance.

Moreover, the evolution of NICU practices over the 2006–2017 study period, including advances in neonatal care and supportive technologies, could independently affect both survival and neurodevelopmental trajectories irrespective of the cord-clamping approach. These temporal changes introduce an inherent risk of confounding, underscoring the need to interpret the findings with caution and to consider the potential impact of practice variation over time.

Recommendation for Future Studies

Current DCC practice is often guided by the newborns' clinical condition, particularly cardiorespiratory status at birth. If a newborn is depressed and not breathing, DCC is usually avoided, potentially depriving vulnerable infants of its benefits. Further research is needed to determine whether resuscitation can be safely performed with the umbilical cord intact and to

evaluate the long-term neurodevelopmental outcomes of this approach in clinically compromised infants.

Future research should evaluate cord clamping strategies in low-resource settings to enhance external validity and global relevance. Such studies are vital to ensure that recommendations are applicable across diverse healthcare systems. Comparative studies are required to explore how the timing of DCC affects the risk of neonatal hypothermia. Trials comparing DCC and ICC should incorporate standardised neurodevelopmental assessment tools to minimise bias and comparability across studies.

Longitudinal studies should extend follow-up into school age, providing a broader understanding of both potential benefits and adverse effects of DCC on long-term neurodevelopment. Current research has not yet established strong links between early life outcomes and later educational attainment (195).

The present study, encompassing diverse maternal and neonatal characteristics, offers a foundation for future research to explore the association between DCC and neurodevelopment in preterm infants. Future works should prioritise multicenter randomised controlled trials with sufficient sample sizes to compare DCC and ICC, generating high-quality evidence to inform clinical guidelines and promote DCC as a standard of care for high-risk preterm infants in Canada and worldwide.

REFERENCES

1. Kramer MS, Papageorghiou A, Culhane J, Bhutta Z, Goldenberg RL, Gravett M, et al. Challenges in defining and classifying the preterm birth syndrome. Am J Obstet Gynecol. February, 2012;206(2):108–12. Epub 20111025. doi: 10.1016/j.ajog.2011.10.864. PubMed PMID: 22118964.
2. Ophelders D, Gussenhoven R, Klein L, Jellema RK, Westerlaken RJJ, Hütten MC, et al. Preterm Brain Injury, Antenatal Triggers, and Therapeutics: Timing Is Key. Cells. August 10, 2020;9(8). Epub 20200810. doi: 10.3390/cells9081871. PubMed PMID: 32785181; PubMed Central PMCID: PMC7464163.
3. McDonald SD, Narvey M, Ehman W, Jain V, Cassell K. Guideline No. 424: Umbilical Cord Management in Preterm and Term Infants. J Obstet Gynaecol Can. March, 2022;44(3):313–22.e1. doi: 10.1016/j.jogc.2022.01.007. PubMed PMID: 35300830.
4. Vitner D, Barrett J, Katherine W, White SW, Newnham JP. Community-based, population-focused preterm birth prevention programs - a review. Arch Gynecol Obstet. December, 2020;302(6):1317–28. Epub 20200901. doi: 10.1007/s00404-020-05759-0. PubMed PMID: 32875346.
5. Tesarz J, Schuster AK, Hermes M, Mildenberger E, Urschitz MS, Treede RD, et al. Associations of preterm birth and neonatal stress exposure with chronic pain in adulthood - Results from the Gutenberg prematurity study. J Psychosom Res. December, 2024;187:111943. Epub 20240924. doi: 10.1016/j.jpsychores.2024.111943. PubMed PMID: 39341156.
6. Walani SR. Global burden of preterm birth. Int J Gynaecol Obstet. July, 2020;150(1):31–3. doi: 10.1002/ijgo.13195. PubMed PMID: 32524596.
7. Shah PS, McDonald SD, Barrett J, Synnes A, Robson K, Foster J, et al. The Canadian Preterm Birth Network: a study protocol for improving outcomes for preterm infants and their families. CMAJ Open. January 18, 2018;6(1):E44–e9. doi: 10.9778/cmajo.20170128. PubMed PMID: 29348260; PubMed Central PMCID: PMC5878956.
8. Dosani A, Sikdar KC, Kumaran M, Kumaran K, Hyderi A, Benlamri A, et al. The paradoxical influence of the COVID-19 lockdown period on different types of preterm births in Alberta: a provincial study. Paediatr Child Health. May, 2024;29(2):90–7. Epub 20230907. doi: 10.1093/pch/pxad063. PubMed PMID: 38586485; PubMed Central PMCID: PMC10996579.
9. Schuermans A, Lewandowski AJ. Understanding the preterm human heart: What do we know so far? Anat Rec (Hoboken). September, 2022;305(9):2099–112. Epub 20220209. doi: 10.1002/ar.24875. PubMed PMID: 35090100; PubMed Central PMCID: PMC9542725.
10. Pascoe L, Burnett AC, Anderson PJ. Cognitive and academic outcomes of children born extremely preterm. Semin Perinatol. December, 2021;45(8):151480. Epub 20210822. doi: 10.1016/j.semperi.2021.151480. PubMed PMID: 34656363.
11. Evensen KAI, Ustad T, Tikanmäki M, Haaramo P, Kajantie E. Long-term motor outcomes of very preterm and/or very low birth weight individuals without cerebral palsy: A review of the current evidence. Semin Fetal Neonatal Med. June, 2020;25(3):101116. Epub 20200520. doi: 10.1016/j.siny.2020.101116. PubMed PMID: 32461044.
12. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Dev Med Child Neurol. April, 2018;60(4):342–55. Epub 20180119. doi: 10.1111/dmcn.13675. PubMed PMID: 29350401.

13. Rogers EE, Hintz SR. Early neurodevelopmental outcomes of extremely preterm infants. Semin Perinatol. December, 2016;40(8):497–509. Epub 20161116. doi: 10.1053/j.semperi.2016.09.002. PubMed PMID: 27865437.
14. Vogel JP, Oladapo OT, Manu A, Gülmezoglu AM, Bahl R. New WHO recommendations to improve the outcomes of preterm birth. Lancet Glob Health. October, 2015;3(10):e589–90. Epub 20150823. doi: 10.1016/s2214-109x(15)00183-7. PubMed PMID: 26310802.
15. Delayed Umbilical Cord Clamping After Birth: ACOG Committee Opinion, Number 814. Obstet Gynecol. December, 2020;136(6):e100–e6. doi: 10.1097/aog.0000000000004167. PubMed PMID: 33214530.
16. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. September 17, 2019;9(9):Cd003248. Epub 20190917. doi: 10.1002/14651858.CD003248.pub4. PubMed PMID: 31529790; PubMed Central PMCID: PMC6748404.
17. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics. October, 2000;106(4):659–71. doi: 10.1542/peds.106.4.659. PubMed PMID: 11015506.
18. Berger TM, Bernet V, El Alama S, Fauchère JC, Hösli I, Irion O, et al. Perinatal care at the limit of viability between 22 and 26 completed weeks of gestation in Switzerland. 2011 revision of the Swiss recommendations. Swiss Med Wkly. October 18, 2011;141:w13280. Epub 20111018. doi: 10.4414/smw.2011.13280. PubMed PMID: 22009720.
19. Yeung T, Ahmed A, Wong J, Toye J, Abou Mehrem A, Mukerji A, et al. Variations in Site-Specific Costs for Infants Born Extremely Preterm in Canadian Neonatal Intensive Care Units. J Pediatr. March, 2024;266:113863. Epub 20231213. doi: 10.1016/j.jpeds.2023.113863. PubMed PMID: 38096975.
20. Myrhaug HT, Brurberg KG, Hov L, Håvelsrud K, Reinar LM. NIPH Systematic Reviews: Executive Summaries. Prognosis and Follow-Up of Extreme Preterm Infants: A Systematic Review. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)
Copyright © 2017 by The Norwegian Institute of Public Health (NIPH). March 23, 2017.
21. Qian Y, Ying X, Wang P, Lu Z, Hua Y. Early versus delayed umbilical cord clamping on maternal and neonatal outcomes. Arch Gynecol Obstet. September, 2019;300(3):531–43. Epub 20190615. doi: 10.1007/s00404-019-05215-8. PubMed PMID: 31203386; PubMed Central PMCID: PMC6694086.
22. Hemmati F, Sharma D, Namavar Jahromi B, Salarian L, Farahbakhsh N. Delayed cord clamping for prevention of intraventricular hemorrhage in preterm neonates: a randomized control trial. J Matern Fetal Neonatal Med. October, 2022;35(19):3633–9. Epub 20201022. doi: 10.1080/14767058.2020.1836148. PubMed PMID: 33092420.
23. Armstrong-Buisseret L, Powers K, Dorling J, Bradshaw L, Johnson S, Mitchell E, et al. Randomised trial of cord clamping at very preterm birth: outcomes at 2 years. Arch Dis Child Fetal Neonatal Ed. August 1, 2020;105(3):292–8. Epub 20190801. doi: 10.1136/archdischild-2019-316912. PubMed PMID: 31371434; PubMed Central PMCID: PMC7363783.
24. Rana N, Kc A, Målqvist M, Subedi K, Andersson O. Effect of Delayed Cord Clamping of Term Babies on Neurodevelopment at 12 Months: A Randomized Controlled Trial. Neonatology. October, 2019;115(1):36–42. Epub 20181002. doi: 10.1159/000491994. PubMed PMID: 30278462.

25. Berg JHM, Isacson M, Basnet O, Gurung R, Subedi K, Kc A, et al. Effect of Delayed Cord Clamping on Neurodevelopment at 3 Years: A Randomized Controlled Trial. Neonatology. July, 2021;118(3):282–8. Epub 20210507. doi: 10.1159/000515838. PubMed PMID: 33965945; PubMed Central PMCID: PMC8491483.
26. The Canadian Neonatal Network™. Toronto, Ontario: Maternal-Infant Care Research Centre, Mount Sinai Hospital, 2022.
27. Zierden HC, Shapiro RL, DeLong K, Carter DM, Ensign LM. Next generation strategies for preventing preterm birth. Adv Drug Deliv Rev. July, 2021;174:190–209. Epub 20210423. doi: 10.1016/j.addr.2021.04.021. PubMed PMID: 33895215; PubMed Central PMCID: PMC8217279.
28. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. May 1, 1998;178(5):1035–40. doi: 10.1016/s0002-9378(98)70544-7. PubMed PMID: 9609580.
29. Baer RJ, Yang J, Berghella V, Chambers CD, Coker TR, Kuppermann M, et al. Risk of preterm birth by maternal age at first and second pregnancy and race/ethnicity. J Perinat Med. July 26, 2018;46(5):539–46. doi: 10.1515/jpm-2017-0014. PubMed PMID: 28455952.
30. Schaaf JM, Liem SM, Mol BW, Abu-Hanna A, Ravelli AC. Ethnic and racial disparities in the risk of preterm birth: a systematic review and meta-analysis. Am J Perinatol. June, 2013;30(6):433–50. Epub 20121011. doi: 10.1055/s-0032-1326988. PubMed PMID: 23059494.
31. Wendt A, Gibbs CM, Peters S, Hogue CJ. Impact of increasing inter-pregnancy interval on maternal and infant health. Paediatr Perinat Epidemiol. July, 2012;26 Suppl 1(0 1):239–58. doi: 10.1111/j.1365-3016.2012.01285.x. PubMed PMID: 22742614; PubMed Central PMCID: PMC4562277.
32. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. January 5, 2008;371(9606):75–84. doi: 10.1016/s0140-6736(08)60074-4. PubMed PMID: 18177778; PubMed Central PMCID: PMC7134569.
33. Muppa L, Bhavadharini K, Ramya A, Bhavadharani R. Preterm Birth: A Review of Its Early Diagnosis and Prevention. Journal of Drug Delivery & Therapeutics. February, 2024;14(2).
34. Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M, Williams JG, et al. Short, medium, and long deferral of umbilical cord clamping compared with umbilical cord milking and immediate clamping at preterm birth: a systematic review and network meta-analysis with individual participant data. Lancet. December 9, 2023;402(10418):2223–34. Epub 20231114. doi: 10.1016/s0140-6736(23)02469-8. PubMed PMID: 37977170.
35. Yaman A, Sharifov K, Memisoglu A, Kandemir I, Arcagok BC, Bilgen HS, et al. Safety of different cord clamping strategies in the early postnatal period. Early Hum Dev. August, 2024;195:106075. Epub 20240710. doi: 10.1016/j.earlhumdev.2024.106075. PubMed PMID: 39002384.
36. Farrar D, Airey R, Law GR, Tuffnell D, Cattle B, Duley L. Measuring placental transfusion for term births: weighing babies with cord intact. Bjog. January, 2011;118(1):70–5. Epub 20101118. doi: 10.1111/j.1471-0528.2010.02781.x. PubMed PMID: 21083868.
37. Moss AJ, Monset-Couchard M. Placental transfusion: early versus late clamping of the umbilical cord. Pediatrics. July, 1967;40(1):109–26. PubMed PMID: 5339450.
38. Arcilla RA, Oh W, Lind J, Gessner IH. Pulmonary arterial pressures of newborn infants born with early and late clamping of the cord. Acta Paediatr Scand. May, 1966;55(3):305–15. doi: 10.1111/j.1651-2227.1966.tb17659.x. PubMed PMID: 5960343.

39. Bhatt S, Alison BJ, Wallace EM, Crossley KJ, Gill AW, Kluckow M, et al. Delaying cord clamping until ventilation onset improves cardiovascular function at birth in preterm lambs. J Physiol. April 15, 2013;591(8):2113–26. Epub 20130211. doi: 10.1113/jphysiol.2012.250084. PubMed PMID: 23401615; PubMed Central PMCID: PMC3634523.
40. Katheria AC, Lakshminrusimha S, Rabe H, McAdams R, Mercer JS. Placental transfusion: a review. J Perinatol. February, 2017;37(2):105–11. Epub 20160922. doi: 10.1038/jp.2016.151. PubMed PMID: 27654493; PubMed Central PMCID: PMC5290307.
41. Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta. Thromb Res. 2004;114(5-6):397–407. doi: 10.1016/j.thromres.2004.06.038. PubMed PMID: 15507270.
42. Lu J, Yue G, Wang Q, Zhou X, Ju R. A review on development of placental transfusion in term and preterm infants. Front Pediatr. September 15, 2022;10:890988. Epub 20220915. doi: 10.3389/fped.2022.890988. PubMed PMID: 36186636; PubMed Central PMCID: PMC9520323.
43. Katheria AC, Brown MK, Rich W, Arnell K. Providing a Placental Transfusion in Newborns Who Need Resuscitation. Front Pediatr. January 25, 2017;5:1. Epub 20170125. doi: 10.3389/fped.2017.00001. PubMed PMID: 28180126; PubMed Central PMCID: PMC5263890.
44. Knol R, Brouwer E, van den Akker T, DeKoninck P, van Geloven N, Polglase GR, et al. Physiological-based cord clamping in very preterm infants - Randomised controlled trial on effectiveness of stabilisation. Resuscitation. December 23, 2020;147:26–33. Epub 20191223. doi: 10.1016/j.resuscitation.2019.12.007. PubMed PMID: 31874212.
45. Badurdeen S, Davis PG, Hooper SB, Donath S, Santomartino GA, Heng A, et al. Physiologically based cord clamping for infants ≥32+0 weeks gestation: A randomised clinical trial and reference percentiles for heart rate and oxygen saturation for infants ≥35+0 weeks gestation. PLoS Med. June 23, 2022;19(6):e1004029. Epub 20220623. doi: 10.1371/journal.pmed.1004029. PubMed PMID: 35737735; PubMed Central PMCID: PMC9269938.
46. Poulos Z, Vandenberg E, Johnson Z, Zahra VA, Lu H, Thiel A, et al. Impact of resuscitation with 100% oxygen during physiological-based cord clamping or immediate cord clamping on lung inflammation and injury. Pediatr Res. August 15, 2025. Epub 20250815. doi: 10.1038/s41390-025-04285-6. PubMed PMID: 40817291.
47. Ghirardello S, Di Tommaso M, Fiocchi S, Locatelli A, Perrone B, Pratesi S, et al. Italian Recommendations for Placental Transfusion Strategies. Front Pediatr. December 3, 2018;6:372. Epub 20181203. doi: 10.3389/fped.2018.00372. PubMed PMID: 30560107; PubMed Central PMCID: PMC6287578.
48. Katheria A, Blank D, Rich W, Finer N. Umbilical cord milking improves transition in premature infants at birth. PLoS One. April 7, 2014;9(4):e94085. Epub 20140407. doi: 10.1371/journal.pone.0094085. PubMed PMID: 24709780; PubMed Central PMCID: PMC3978008.
49. Katheria A, Szychowski J, Carlo WA, Subramaniam A, Reister F, Essers J, et al. Umbilical Cord Milking Versus Delayed Cord Clamping in Infants 28 to 32 Weeks: A Randomized Trial. Pediatrics. Dec 1, 2023;152(6). doi: 10.1542/peds.2023-063113. PubMed PMID: 37941523; PubMed Central PMCID: PMC12207594.
50. Rao NN, Prakash KP, Nyamagoudar A. A randomised controlled trial comparing umbilical cord milking to delayed cord clamping at birth in preterm infants 28-36 weeks gestational age. Eur J Pediatr. June, 2024;183(6):2791–6. Epub 20240406. doi: 10.1007/s00431-024-05550-2. PubMed PMID: 38581461.

51. Kuitunen I, Haapanen M, Kekki M, Kiviranta P. Umbilical cord management strategies and risk of intraventricular haemorrhage in preterm neonates: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. October 5, 2025. Epub 20251005. doi: 10.1136/archdischild-2025-329006. PubMed PMID: 41047166.
52. Surak A, Elsayed Y. Delayed cord clamping: Time for physiologic implementation. J Neonatal Perinatal Med. 2022;15(1):19–27. doi: 10.3233/npm-210745. PubMed PMID: 34219673.
53. Ramji S. Delayed Cord Clamping and Umbilical Cord Milking at Birth. Indian Pediatr. September, 2015;52(9):749. PubMed PMID: 26519706.
54. Brocato B, Holliday N, Whitehurst RM, Jr., Lewis D, Varner S. Delayed Cord Clamping in Preterm Neonates: A Review of Benefits and Risks. Obstet Gynecol Surv. January, 2016;71(1):39–42. doi: 10.1097/ogx.0000000000000263. PubMed PMID: 26819134.
55. Finnemore A, Groves A. Physiology of the fetal and transitional circulation. Semin Fetal Neonatal Med. August, 2015;20(4):210–6. Epub 20150425. doi: 10.1016/j.siny.2015.04.003. PubMed PMID: 25921445.
56. Bensley JG, De Matteo R, Harding R, Black MJ. The effects of preterm birth and its antecedents on the cardiovascular system. Acta Obstet Gynecol Scand. June, 2016;95(6):652–63. Epub 20160331. doi: 10.1111/aogs.12880. PubMed PMID: 26918772.
57. Niermeyer S. A physiologic approach to cord clamping: Clinical issues. Matern Health Neonatol Perinatol. September 8, 2015;1:21. Epub 20150908. doi: 10.1186/s40748-015-0022-5. PubMed PMID: 27057338; PubMed Central PMCID: PMC4823683.
58. Kluckow M, Hooper SB. Using physiology to guide time to cord clamping. Semin Fetal Neonatal Med. August, 2015;20(4):225–31. Epub 20150327. doi: 10.1016/j.siny.2015.03.002. PubMed PMID: 25818878.
59. Yao AC, Lind J. Effect of gravity on placental transfusion. Lancet. September 6, 1969;2(7619):505–8. doi: 10.1016/s0140-6736(69)90213-x. PubMed PMID: 4184835.
60. Seidler AL, Libesman S, Hunter KE, Barba A, Aberoumand M, Williams JG, et al. Short, medium, and long deferral of umbilical cord clamping compared with umbilical cord milking and immediate clamping at preterm birth: a systematic review and network meta-analysis with individual participant data. Lancet. November 14, 2023;402(10418):2223–34. Epub 20231114. doi: 10.1016/s0140-6736(23)02469-8. PubMed PMID: 37977170.
61. Noori S, Stavroudis TA, Seri I. Systemic and cerebral hemodynamics during the transitional period after premature birth. Clin Perinatol. December, 2009;36(4):723–36, v. doi: 10.1016/j.clp.2009.07.015. PubMed PMID: 19944832.
62. Doherty TM, Hu A, Salik I. Physiology, Neonatal. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2025, StatPearls Publishing LLC.; January, 2025.
63. Wang ZM, Zhou JY, Tang W, Jiang YY, Wang R, Wang LS. Effect of Placental Transfusion on Long-Term Neurodevelopmental Outcomes in Premature Infants: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pediatr Neurol. May, 2024;154:20–5. Epub 20240201. doi: 10.1016/j.pediatrneurol.2024.01.018. PubMed PMID: 38452434.
64. Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, et al. Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis. Lancet. December 9, 2023;402(10418):2209–22. Epub 20231114. doi: 10.1016/s0140-6736(23)02468-6. PubMed PMID: 37977169.

65. Raju TN. Timing of umbilical cord clamping after birth for optimizing placental transfusion. Curr Opin Pediatr. April, 2013;25(2):180–7. doi: 10.1097/MOP.0b013e32835d2a9e. PubMed PMID: 23407180.
66. Sorin G, Tosello B. [Focus on placental transfusion for preterm neonates: Delayed cord clamping and/or milking?]. Gynecol Obstet Fertil. November, 2016;44(11):641–6. Epub 20160913. doi: 10.1016/j.gyobfe.2016.08.002. PubMed PMID: 27638229.
67. Fogarty M, Osborn DA, Askie L, Seidler AL, Hunter K, Lui K, et al. Delayed vs early umbilical cord clamping for preterm infants: a systematic review and meta-analysis. Am J Obstet Gynecol. January, 2018;218(1):1–18. Epub 20171030. doi: 10.1016/j.ajog.2017.10.231. PubMed PMID: 29097178.
68. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. September, 2010;126(3):443–56. Epub 20100823. doi: 10.1542/peds.2009-2959. PubMed PMID: 20732945; PubMed Central PMCID: PMC2982806.
69. Yadav S, Lee B. Neonatal Respiratory Distress Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2025, StatPearls Publishing LLC.; July 25, 2025.
70. Baseer KAA, Mohamed M, Abd-Elmawgood EA. Risk Factors of Respiratory Diseases Among Neonates in Neonatal Intensive Care Unit of Qena University Hospital, Egypt. Ann Glob Health. February 26, 2020;86(1):22. Epub 20200226. doi: 10.5334/aogh.2739. PubMed PMID: 32140431; PubMed Central PMCID: PMC7047767.
71. Wachtel EV, Zaccario M, Mally P. Impact of Respiratory Morbidities on Neurodevelopmental Outcome of Late Preterm Infants. Am J Perinatol. October, 2015;32(12):1164–8. Epub 20150515. doi: 10.1055/s-0035-1551673. PubMed PMID: 25978842.
72. Cannavò L, Perrone S, Viola V, Marseglia L, Di Rosa G, Gitto E. Oxidative Stress and Respiratory Diseases in Preterm Newborns. Int J Mol Sci. November 19, 2021;22(22). Epub 20211119. doi: 10.3390/ijms222212504. PubMed PMID: 34830385; PubMed Central PMCID: PMC8625766.
73. Sun H, Zhou Y, Xiong H, Kang W, Xu B, Liu D, et al. Prognosis of very preterm infants with severe respiratory distress syndrome receiving mechanical ventilation. Lung. April, 2015;193(2):249–54. Epub 20150113. doi: 10.1007/s00408-014-9683-5. PubMed PMID: 25583617.
74. Kakkilaya V, Pramanik AK, Ibrahim H, Hussein S. Effect of placental transfusion on the blood volume and clinical outcome of infants born by cesarean section. Clin Perinatol. September, 2008;35(3):561–70, xi. doi: 10.1016/j.clp.2008.07.002. PubMed PMID: 18952022.
75. García C, Prieto MT, Escudero F, Bosh-Giménez V, Quesada L, Lewanczyk M, et al. The impact of early versus delayed cord clamping on hematological and cardiovascular changes in preterm newborns between 24 and 34 weeks' gestation: a randomized clinical trial. Arch Gynecol Obstet. June, 2024;309(6):2483–90. Epub 20230712. doi: 10.1007/s00404-023-07119-0. PubMed PMID: 37436461.
76. Hwang JS, Rehan VK. Recent Advances in Bronchopulmonary Dysplasia: Pathophysiology, Prevention, and Treatment. Lung. April, 2018;196(2):129–38. Epub 20180127. doi: 10.1007/s00408-018-0084-z. PubMed PMID: 29374791; PubMed Central PMCID: PMC5856637.

77. McEvoy CT, Aschner JL. The Natural History of Bronchopulmonary Dysplasia: The Case for Primary Prevention. Clin Perinatol. December, 2015;42(4):911–31. Epub 20151001. doi: 10.1016/j.clp.2015.08.014. PubMed PMID: 26593086; PubMed Central PMCID: PMC4662069.
78. Lodha A, Sauvé R, Bhandari V, Tang S, Christianson H, Bhandari A, et al. Need for supplemental oxygen at discharge in infants with bronchopulmonary dysplasia is not associated with worse neurodevelopmental outcomes at 3 years corrected age. PLoS One. March 19, 2014;9(3):e90843. Epub 20140319. doi: 10.1371/journal.pone.0090843. PubMed PMID: 24646665; PubMed Central PMCID: PMC3960119.
79. Owen LS, Manley BJ, Hodgson KA, Roberts CT. Impact of early respiratory care for extremely preterm infants. Semin Perinatol. December, 2021;45(8):151478. Epub 20210821. doi: 10.1016/j.semperi.2021.151478. PubMed PMID: 34474939.
80. Patel M, Gopalakrishnan M, Sundararajan S. Impact of Delayed Cord Clamping on Red Blood Cell Transfusion and Related Outcomes in Very Low Birth Weight Infants. Am J Perinatol. May, 2024;41(S 01):e2444–e53. Epub 20230622. doi: 10.1055/a-2115-4360. PubMed PMID: 37348546.
81. Conrad C, Newberry D. Understanding the Pathophysiology, Implications, and Treatment Options of Patent Ductus Arteriosus in the Neonatal Population. Adv Neonatal Care. June, 2019;19(3):179–87. doi: 10.1097/anc.0000000000000590. PubMed PMID: 30720481.
82. Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, et al. Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g. Pediatrics. August, 2017;140(2). Epub 20170712. doi: 10.1542/peds.2016-4258. PubMed PMID: 28701390.
83. Hamrick SEG, Sallmon H, Rose AT, Porras D, Shelton EL, Reese J, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics. November, 2020;146(5). doi: 10.1542/peds.2020-1209. PubMed PMID: 33093140; PubMed Central PMCID: PMC7605084.
84. Humberg A, Fortmann I, Siller B, Kopp MV, Herting E, Göpel W, et al. Preterm birth and sustained inflammation: consequences for the neonate. Semin Immunopathol. August, 2020;42(4):451–68. Epub 20200713. doi: 10.1007/s00281-020-00803-2. PubMed PMID: 32661735; PubMed Central PMCID: PMC7508934.
85. Glaser MA, Hughes LM, Jnah A, Newberry D. Neonatal Sepsis: A Review of Pathophysiology and Current Management Strategies. Adv Neonatal Care. February, 2021;21(1):49–60. doi: 10.1097/anc.0000000000000769. PubMed PMID: 32956076.
86. Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at ≥35 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics. December, 2018;142(6). doi: 10.1542/peds.2018-2894. PubMed PMID: 30455342.
87. Alshaikh B, Yee W, Lodha A, Henderson E, Yusuf K, Sauve R. Coagulase-negative staphylococcus sepsis in preterm infants and long-term neurodevelopmental outcome. J Perinatol. February, 2014;34(2):125–9. Epub 20131219. doi: 10.1038/jp.2013.155. PubMed PMID: 24355942.
88. Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al. Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture-negative conditions. Arch Dis Child Fetal Neonatal Ed. September, 2021;106(5):467–73. Epub 20210121. doi: 10.1136/archdischild-2020-320664. PubMed PMID: 33478957; PubMed Central PMCID: PMC8292446.
89. Adams-Chapman I. Long-term impact of infection on the preterm neonate. Semin Perinatol. December, 2012;36(6):462–70. doi: 10.1053/j.semperi.2012.06.009. PubMed PMID: 23177806.

90. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. Jama. November 17, 2004;292(19):2357–65. doi: 10.1001/jama.292.19.2357. PubMed PMID: 15547163.
91. Chiruvolu A, Elliott E, Rich D, Stone GL, Qin H, Inzer RW. Effect of delay in cord clamping 45 versus 6 s on very preterm singleton infants. Early Hum Dev. April, 2018;119:15–8. Epub 20180305. doi: 10.1016/j.earlhumdev.2018.02.021. PubMed PMID: 29518646.
92. Lodha A, Shah PS, Soraisham AS, Rabi Y, Abou Mehrem A, Singhal N. Association of Deferred vs Immediate Cord Clamping With Severe Neurological Injury and Survival in Extremely Low-Gestational-Age Neonates. JAMA Netw Open. March, 2019;2(3):e191286. Epub 20190301. doi: 10.1001/jamanetworkopen.2019.1286. PubMed PMID: 30924898; PubMed Central PMCID: PMC6450317.
93. Huang J, Wang Y, Tian T, Zhu T, Tang J, Gao Q, et al. Risk factors for periventricular-intraventricular haemorrhage severity in preterm infants: a propensity score-matched analysis. BMC Pediatr. July 5, 2023;23(1):341. Epub 20230705. doi: 10.1186/s12887-023-04114-x. PubMed PMID: 37407929; PubMed Central PMCID: PMC10320876.
94. McCauley KE, Carey EC, Weaver AL, Mara KC, Clark RH, Carey WA, et al. Survival of Ventilated Extremely Premature Neonates With Severe Intraventricular Hemorrhage. Pediatrics. April, 2021;147(4). Epub 20210316. doi: 10.1542/peds.2020-1584. PubMed PMID: 33727247; PubMed Central PMCID: PMC8015160.
95. Siffel C, Kistler KD, Sarda SP. Global incidence of intraventricular hemorrhage among extremely preterm infants: a systematic literature review. J Perinat Med. March 19, 2021;49(9):1017–26. Epub 20210319. doi: 10.1515/jpm-2020-0331. PubMed PMID: 33735943.
96. Diwakar K, Hader WJ, Soraisham A, Amin H, Tang S, Bullivant K, et al. Long-Term Neurodevelopmental and Growth Outcomes of Premature Infants Born at <29 week Gestational Age with Post-Hemorrhagic Hydrocephalus Treated with Ventriculo-Peritoneal Shunt. Indian J Pediatr. September, 2017;84(9):662–9. Epub 20170403. doi: 10.1007/s12098-017-2319-z. PubMed PMID: 28367615.
97. Hollebrandse NL, Spittle AJ, Burnett AC, Anderson PJ, Roberts G, Doyle LW, et al. School-age outcomes following intraventricular haemorrhage in infants born extremely preterm. Arch Dis Child Fetal Neonatal Ed. January, 2021;106(1):4–8. Epub 20200730. doi: 10.1136/archdischild-2020-318989. PubMed PMID: 32732377.
98. Tréluyer L, Chevallier M, Jarreau PH, Baud O, Benhammou V, Gire C, et al. Intraventricular Hemorrhage in Very Preterm Children: Mortality and Neurodevelopment at Age 5. Pediatrics. April 1, 2023;151(4). doi: 10.1542/peds.2022-059138. PubMed PMID: 36919442; PubMed Central PMCID: PMC10071431.
99. Vesoulis ZA, Liao SM, Mathur AM. Delayed cord clamping is associated with improved dynamic cerebral autoregulation and decreased incidence of intraventricular hemorrhage in preterm infants. J Appl Physiol (1985). July, 2019;127(1):103–10. Epub 20190502. doi: 10.1152/japplphysiol.00049.2019. PubMed PMID: 31046516; PubMed Central PMCID: PMC6692745.
100. Katheria A, Reister F, Essers J, Mendler M, Hummler H, Subramaniam A, et al. Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants. Jama. November 19, 2019;322(19):1877–86. doi: 10.1001/jama.2019.16004. PubMed PMID: 31742630; PubMed Central PMCID: PMC6865839.

101. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res. November, 2001;50(5):553–62. doi: 10.1203/00006450-200111000-00003. PubMed PMID: 11641446.
102. Ng NS, Razak A, Chandrasekharan P, McLean G, Sackett V, Zhou L, et al. Early neurodevelopmental outcomes of preterm infants with intraventricular haemorrhage and periventricular leukomalacia. J Paediatr Child Health. August 26, 2024;60(11):669–74. Epub 20240826. doi: 10.1111/jpc.16654. PubMed PMID: 39183581.
103. Leite SS, Matos J, Grenha J, Braga AC, Rocha R. Neurodevelopmental outcomes of children with periventricular leukomalacia: the role of infection and ischemia. Journal of Pediatric and Neonatal Individualized Medicine (JPNIM). April 30, 2021;10(1):e100105–e.
104. Jacobson LK, Dutton GN. Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. Surv Ophthalmol. July – August, 2000;45(1):1–13. doi: 10.1016/s0039-6257(00)00134-x. PubMed PMID: 10946078.
105. Novak CM, Ozen M, Burd I. Perinatal Brain Injury: Mechanisms, Prevention, and Outcomes. Clin Perinatol. June, 2018;45(2):357–75. Epub 20180321. doi: 10.1016/j.clp.2018.01.015. PubMed PMID: 29747893.
106. Shah PS, Norman M, Rusconi F, Kusuda S, Reichman B, Battin M, et al. Five-minute Apgar score and outcomes in neonates of 24-28 weeks' gestation. Arch Dis Child Fetal Neonatal Ed. July, 2022;107(4):437–46. Epub 20211115. doi: 10.1136/archdischild-2021-322230. PubMed PMID: 34782368.
107. Hwang-Bo S, Seo YM, Oh MY, Im SA, Youn YA. The prognosis of refractory hypotension and severe intraventricular hemorrhage in very low birth weight infants. Medicine (Baltimore). July 29, 2022;101(30):e29598. Epub 20220729. doi: 10.1097/md.0000000000029598. PubMed PMID: 35905281; PubMed Central PMCID: PMC9333540.
108. Zhang LP, Lei XP, Luo LJ, Dong WB. Risk factors for necrotizing enterocolitis in very preterm infants: a case-control study in southwest China. J Matern Fetal Neonatal Med. March, 2019;32(6):896–901. Epub 20171102. doi: 10.1080/14767058.2017.1395011. PubMed PMID: 29096567.
109. Lee JY, Park KH, Kim A, Yang HR, Jung EY, Cho SH. Maternal and Placental Risk Factors for Developing Necrotizing Enterocolitis in Very Preterm Infants. Pediatr Neonatol. February, 2017;58(1):57–62. Epub 20160529. doi: 10.1016/j.pedneo.2016.01.005. PubMed PMID: 27328638.
110. Bruno MA, Galletti MF, Brener Dik PH, Mariani GL, Gonzalez Á, Nieto R. Prevalence and risk factors associated with the need for surgical intervention due to necrotizing enterocolitis in very low birth weight infants. Early Hum Dev. January, 2024;188:105917. Epub 20231210. doi: 10.1016/j.earlhumdev.2023.105917. PubMed PMID: 38096735.
111. Hu X, Liang H, Li F, Zhang R, Zhu Y, Zhu X, et al. Necrotizing enterocolitis: current understanding of the prevention and management. Pediatr Surg Int. January 10, 2024;40(1):32. Epub 20240110. doi: 10.1007/s00383-023-05619-3. PubMed PMID: 38196049; PubMed Central PMCID: PMC10776729.
112. Patel AL, Panagos PG, Silvestri JM. Reducing Incidence of Necrotizing Enterocolitis. Clin Perinatol. September, 2017;44(3):683–700. Epub 20170705. doi: 10.1016/j.clp.2017.05.004. PubMed PMID: 28802346.
113. Garg BD, Kabra NS, Bansal A. Role of delayed cord clamping in prevention of necrotizing enterocolitis in preterm neonates: a systematic review. J Matern Fetal Neonatal Med. January,

2019;32(1):164–72. Epub 20170831. doi: 10.1080/14767058.2017.1370704. PubMed PMID: 28826265.
114. Quimson SK. Retinopathy of Prematurity: Pathogenesis and Current Treatment Options. Neonatal Netw. 2015;34(5):284–7. doi: 10.1891/0730-0832.34.5.284. PubMed PMID: 26802829.
115. Dai Y, Zhu L, Zhou Y, Wu Y, Chen D, Wang R, et al. Incidence of retinopathy of prematurity treatment in extremely preterm infants in China. Paediatr Perinat Epidemiol. May, 2022;36(3):380–9. Epub 20210901. doi: 10.1111/ppe.12810. PubMed PMID: 34467552.
116. Fortes Filho JB, Eckert GU, Valiatti FB, Dos Santos PG, da Costa MC, Procianoy RS. The influence of gestational age on the dynamic behavior of other risk factors associated with retinopathy of prematurity (ROP). Graefes Arch Clin Exp Ophthalmol. June, 2010;248(6):893–900. Epub 20091217. doi: 10.1007/s00417-009-1248-6. PubMed PMID: 20016911; PubMed Central PMCID: PMC2859157.
117. Dutta S, Narang S, Narang A, Dogra M, Gupta A. Risk factors of threshold retinopathy of prematurity. Indian Pediatr. July, 2004;41(7):665–71. PubMed PMID: 15297681.
118. Allred EN, Capone A, Jr., Fraioli A, Dammann O, Droste P, Duker J, et al. Retinopathy of prematurity and brain damage in the very preterm newborn. J aapos. June, 2014;18(3):241–7. doi: 10.1016/j.jaapos.2014.01.014. PubMed PMID: 24924276; PubMed Central PMCID: PMC4057649.
119. Song D, Jegatheesan P, DeSandre G, Govindaswami B. Duration of Cord Clamping and Neonatal Outcomes in Very Preterm Infants. PLoS One. September 21, 2015;10(9):e0138829. Epub 20150921. doi: 10.1371/journal.pone.0138829. PubMed PMID: 26390401; PubMed Central PMCID: PMC4577121.
120. Kling PJ. Iron Nutrition, Erythrocytes, and Erythropoietin in the NICU: Erythropoietic and Neuroprotective Effects. Neoreviews. February, 2020;21(2):e80–e8. doi: 10.1542/neo.21-2-e80. PubMed PMID: 32005718.
121. Banerjee J, Asamoah FK, Singhvi D, Kwan AW, Morris JK, Aladangady N. Haemoglobin level at birth is associated with short term outcomes and mortality in preterm infants. BMC Med. January 27, 2015;13:16. Epub 20150127. doi: 10.1186/s12916-014-0247-6. PubMed PMID: 25622597; PubMed Central PMCID: PMC4307132.
122. Handley SC, Kumbhat N, Eggleston B, Foglia EE, Davis AS, Van Meurs K, et al. Exposure to umbilical cord management approaches and death or neurodevelopmental impairment at 22-26 months' corrected age after extremely preterm birth. Arch Dis Child Fetal Neonatal Ed. May, 2023;108(3):224–31. Epub 20221017. doi: 10.1136/archdischild-2022-324565. PubMed PMID: 36253076; PubMed Central PMCID: PMC10108713.
123. Mercer JS, Erickson-Owens DA, Deoni SCL, Dean Iii DC, Tucker R, Parker AB, et al. The Effects of Delayed Cord Clamping on 12-Month Brain Myelin Content and Neurodevelopment: A Randomized Controlled Trial. Am J Perinatol. January, 2022;39(1):37–44. Epub 20200721. doi: 10.1055/s-0040-1714258. PubMed PMID: 32702760; PubMed Central PMCID: PMC9800052.
124. Mercer JS, Vohr BR, Erickson-Owens DA, Padbury JF, Oh W. Seven-month developmental outcomes of very low birth weight infants enrolled in a randomized controlled trial of delayed versus immediate cord clamping. J Perinatol. Jan, 2010;30(1):11–6. Epub 20091022. doi: 10.1038/jp.2009.170. PubMed PMID: 19847185; PubMed Central PMCID: PMC2799542.
125. Berg JHM, Isacson M, Basnet O, Gurung R, Subedi K, Kc A, et al. Effect of Delayed Cord Clamping on Neurodevelopment at 3 Years: A Randomized Controlled Trial. Neonatology. May

7, 2021;118(3):282–8. Epub 20210507. doi: 10.1159/000515838. PubMed PMID: 33965945; PubMed Central PMCID: PMC8491483.
126. Kim J, Suen HK. Predicting children's academic achievement from early assessment scores: A validity generalization study. Early Childhood Research Quarterly. December 1, 2003;18(4):547–66.
127. Wong HS, Santhakumaran S, Cowan FM, Modi N. Developmental Assessments in Preterm Children: A Meta-analysis. Pediatrics. August, 2016;138(2). doi: 10.1542/peds.2016-0251. PubMed PMID: 27471220.
128. Doucette SM, Tang S, Kehler H, Creighton D, Lodha A. Utility of the 21-month neurodevelopmental outcome for predicting neurodevelopmental impairment at 36 months for preterm infants <29 weeks gestation. J Perinatol. November, 2023;43(11):1406–12. Epub 20230915. doi: 10.1038/s41372-023-01777-3. PubMed PMID: 37714894.
129. Rabe H, Sawyer A, Amess P, Ayers S. Neurodevelopmental Outcomes at 2 and 3.5 Years for Very Preterm Babies Enrolled in a Randomized Trial of Milking the Umbilical Cord versus Delayed Cord Clamping. Neonatology. 2016;109(2):113–9. Epub 20151210. doi: 10.1159/000441891. PubMed PMID: 26650133.
130. Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. JAMA Pediatr. July, 2015;169(7):631–8. doi: 10.1001/jamapediatrics.2015.0358. PubMed PMID: 26010418.
131. Mercer JS, Erickson-Owens DA, Vohr BR, Tucker RJ, Parker AB, Oh W, et al. Effects of Placental Transfusion on Neonatal and 18 Month Outcomes in Preterm Infants: A Randomized Controlled Trial. J Pediatr. January, 2016;168:50–5.e1. Epub 20151104. doi: 10.1016/j.jpeds.2015.09.068. PubMed PMID: 26547399; PubMed Central PMCID: PMC4698069.
132. Chiruvolu A, Mallett LH, Govande VP, Raju VN, Hammonds K, Katheria AC. Variations in umbilical cord clamping practices in the United States: a national survey of neonatologists. J Matern Fetal Neonatal Med. October, 2022;35(19):3646–52. Epub 20201020. doi: 10.1080/14767058.2020.1836150. PubMed PMID: 33081557.
133. Shah D. Healthy worker effect phenomenon. Indian J Occup Environ Med. August, 2009;13(2):77–9. doi: 10.4103/0019-5278.55123. PubMed PMID: 20386623; PubMed Central PMCID: PMC2847330.
134. Moe AM, Kurilova J, Afzal AR, Benzies KM. Effects of Alberta Family Integrated Care (FICare) on Preterm Infant Development: Two Studies at 2 Months and between 6 and 24 Months Corrected Age. J Clin Med. 2022;11(6). Epub 20220318. doi: 10.3390/jcm11061684. PubMed PMID: 35330009; PubMed Central PMCID: PMC8952230.
135. Foundation CH. Because of you, Calgary is leading preterm birth research! Available from: https://www.calgaryhealthfoundation.ca/our-blog/calgary-leading-preterm-birth-research/.
136. Newswire G. $10M investment from the Taylor Family Foundation ensures a bright future for Southern Alberta's critically-ill newborns. Torinto: The Canadian Press; Nov 16, 2022 [cited 2022]. Available from: https://www.thecanadianpressnews.ca/globenewswire_press_releases/10m-investment-from-the-taylor-family-foundation-ensures-a-bright-future-for-southern-alberta-s/article_5e0db8c2-25f3-5a4c-8248-427f0143322d.html.

137. Kelsey J, Whittemore A, Evans A, Thompson W. Prospective cohort studies: planning and execution. Methods in observational epidemiology, 2nd ed New York: Oxford University Press. 1996:87–112.
138. Philippe Gamache DH, Christine Blaser. Material and social deprivation index: A summary2020.
139. Fidler V, Nagelkerke N. The Mantel-Haenszel procedure revisited: models and generalizations. PLoS One. March 13, 2013;8(3):e58327. Epub 20130313. doi: 10.1371/journal.pone.0058327. PubMed PMID: 23516463; PubMed Central PMCID: PMC3596394.
140. Sperandei S. Understanding logistic regression analysis. Biochem Med (Zagreb). February 15, 2014;24(1):12–8. Epub 20140215. doi: 10.11613/bm.2014.003. PubMed PMID: 24627710; PubMed Central PMCID: PMC3936971.
141. Groenwold RH, Klungel OH, Grobbee DE, Hoes AW. Selection of confounding variables should not be based on observed associations with exposure. European journal of epidemiology. August, 2011;26:589–93.
142. Paul P, Pennell ML, Lemeshow S. Standardizing the power of the Hosmer-Lemeshow goodness of fit test in large data sets. Stat Med. January 15, 2013;32(1):67–80. Epub 20120726. doi: 10.1002/sim.5525. PubMed PMID: 22833304.
143. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. March – April, 2011;10(2):150–61. doi: 10.1002/pst.433. PubMed PMID: 20925139; PubMed Central PMCID: PMC3120982.
144. Engle WA. Age terminology during the perinatal period. Pediatrics. November, 2004;114(5):1362–4. doi: 10.1542/peds.2004-1915. PubMed PMID: 15520122.
145. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. September,1991;119(3):417–23. doi: 10.1016/s0022-3476(05)82056-6. PubMed PMID: 1880657.
146. Kim MA, Han GH, Kim YH. Prediction of small-for-gestational age by fetal growth rate according to gestational age. PLoS One. April 26, 2019;14(4):e0215737. Epub 20190426. doi: 10.1371/journal.pone.0215737. PubMed PMID: 31026299; PubMed Central PMCID: PMC6485641.
147. Fraser J, Walls M, McGuire W. Respiratory complications of preterm birth. Bmj. October 23, 2004;329(7472):962–5. doi: 10.1136/bmj.329.7472.962. PubMed PMID: 15499114; PubMed Central PMCID: PMC524111.
148. Schmidt AR, Ramamoorthy C. Bronchopulmonary dysplasia. Paediatr Anaesth. February, 2022;32(2):174–80. Epub 20211215. doi: 10.1111/pan.14365. PubMed PMID: 34877749.
149. Abu-Shaweesh JM, Almidani E. PDA: Does it matter? Int J Pediatr Adolesc Med. December, 2020;7(1):9–12. Epub 20191203. doi: 10.1016/j.ijpam.2019.12.001. PubMed PMID: 32373696; PubMed Central PMCID: PMC7193069.
150. Ballabh P, de Vries LS. White matter injury in infants with intraventricular haemorrhage: mechanisms and therapies. Nat Rev Neurol. April, 2021;17(4):199–214. Epub 20210127. doi: 10.1038/s41582-020-00447-8. PubMed PMID: 33504979; PubMed Central PMCID: PMC8880688.
151. Sheehan JW, Pritchard M, Heyne RJ, Brown LS, Jaleel MA, Engle WD, et al. Severe intraventricular hemorrhage and withdrawal of support in preterm infants. J Perinatol. April, 2017;37(4):441–7. Epub 20161215. doi: 10.1038/jp.2016.233. PubMed PMID: 27977011.

152. Reddy N, Doyle M, Hanagandi P, Taranath A, Dahmoush H, Krishnan P, et al. Neuroradiological Mimics of Periventricular Leukomalacia. J Child Neurol. February, 2022;37(2):151–67. Epub 20211222. doi: 10.1177/08830738211026052. PubMed PMID: 34937403.
153. Shah PS, Barrett J, Claveau M, Cieslak Z, Makary H, Monterrosa L, et al. Association of umbilical cord blood gas values with mortality and severe neurologic injury in preterm neonates <29 weeks' gestation: a national cohort study. Am J Obstet Gynecol. July, 2022;227(1):85.e1–.e10. Epub 20220106. doi: 10.1016/j.ajog.2022.01.001. PubMed PMID: 34999082.
154. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. July 8, 2021;128(10):e51–e68. Epub 20210708. doi: 10.1016/j.ophtha.2021.05.031. PubMed PMID: 34247850; PubMed Central PMCID: PMC10979521.
155. Hong EH, Shin YU, Cho H. Retinopathy of prematurity: a review of epidemiology and current treatment strategies. Clin Exp Pediatr. October 12, 2022;65(3):115–26. Epub 20211012. doi: 10.3345/cep.2021.00773. PubMed PMID: 34645255; PubMed Central PMCID: PMC8898617.
156. Katheria A, Garey D, Truong G, Akshoomoff N, Steen J, Maldonado M, et al. A Randomized Clinical Trial of Umbilical Cord Milking vs Delayed Cord Clamping in Preterm Infants: Neurodevelopmental Outcomes at 22-26 Months of Corrected Age. J Pediatr. March, 2018;194:76–80. Epub 20171212. doi: 10.1016/j.jpeds.2017.10.037. PubMed PMID: 29246467; PubMed Central PMCID: PMC9442450.
157. Renaud F, Béliveau MJ, Akzam-Ouellette MA, Jauvin K, Labelle F. Comparison of the Wechsler Preschool and Primary Scale of Intelligence-Third Edition and the Leiter-R Intellectual Assessments for Clinic-Referred Children. J Psychoeduc Assess. September, 2022;40(7):825–38. Epub 20220527. doi: 10.1177/07342829221105388. PubMed PMID: 36110225; PubMed Central PMCID: PMC9465540.
158. Paulson A, Vargus-Adams J. Overview of Four Functional Classification Systems Commonly Used in Cerebral Palsy. Children (Basel). April 24, 2017;4(4). Epub 20170424. doi: 10.3390/children4040030. PubMed PMID: 28441773; PubMed Central PMCID: PMC5406689.
159. van Dyk J, Church P, Dell S, To T, Luther M, Shah V. Prediction of long-term neurodevelopmental outcome in preterm infants using trajectories of general movement assessments. J Perinatol. October, 2018;38(10):1398–406. Epub 20180727. doi: 10.1038/s41372-018-0173-0. PubMed PMID: 30054588.
160. Lind A, Korkman M, Lehtonen L, Lapinleimu H, Parkkola R, Matomäki J, et al. Cognitive and neuropsychological outcomes at 5 years of age in preterm children born in the 2000s. Dev Med Child Neurol. March, 2011;53(3):256–62. Epub 20101217. doi: 10.1111/j.1469-8749.2010.03828.x. PubMed PMID: 21166668.
161. Society. DoCaCP. A Health Professional's Guide for using the WHO GROWTH CHARTS FOR CANADA 2014 [updated 2014; cited 2010]. Available from: https://www.dietitians.ca/DietitiansOfCanada/media/Documents/WHO%20Growth%20Charts/2014-A-Health-Professionals-Guide-to-Using-the-Charts.pdf.
162. Peng H, Yang J, Wang D, Guo F, Hou Y, Yin A. Outcomes of pregnancies with trisomy 16 mosaicism detected by NIPT: a series of case reports. Mol Cytogenet. September 20, 2021;14(1):44. Epub 20210920. doi: 10.1186/s13039-021-00559-w. PubMed PMID: 34544454; PubMed Central PMCID: PMC8454120.

163. Walden RV, Taylor SC, Hansen NI, Poole WK, Stoll BJ, Abuelo D, et al. Major congenital anomalies place extremely low birth weight infants at higher risk for poor growth and developmental outcomes. Pediatrics. December, 2007;120(6):e1512–9. Epub 20071105. doi: 10.1542/peds.2007-0354. PubMed PMID: 17984212.
164. Klinger G, Bromiker R, Zaslavsky-Paltiel I, Sokolover N, Lerner-Geva L, Yogev Y, et al. Antepartum Hemorrhage and Outcome of Very Low Birth Weight, Very Preterm Infants: A Population-Based Study. Am J Perinatol. September, 2021;38(11):1134–41. Epub 20200523. doi: 10.1055/s-0040-1710353. PubMed PMID: 32446258.
165. Chambers GM, Venetis CA, Jorm LR, Stavrou EP, Vajdic CM. Parity: A key measure of confounding in data-linkage studies of outcomes after medically assisted reproduction. Int J Popul Data Sci. March 16, 2020;5(1):1119. Epub 20200316. doi: 10.23889/ijpds.v5i1.1119. PubMed PMID: 32935047; PubMed Central PMCID: PMC7473264.
166. Daruich A, Bremond-Gignac D, Behar-Cohen F, Kermorvant E. [Retinopathy of prematurity: from prevention to treatment]. Med Sci (Paris). October, 2020;36(10):900–7. Epub 20201007. doi: 10.1051/medsci/2020163. PubMed PMID: 33026333.
167. Pierrat V, Marchand-Martin L, Marret S, Arnaud C, Benhammou V, Cambonie G, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. Bmj. April, 2021;373:n741. Epub 20210428. doi: 10.1136/bmj.n741. PubMed PMID: 33910920; PubMed Central PMCID: PMC8080137.
168. Del Rosario C, Slevin M, Molloy EJ, Quigley J, Nixon E. How to use the Bayley Scales of Infant and Toddler Development. Arch Dis Child Educ Pract Ed. April, 2021;106(2):108–12. Epub 20200828. doi: 10.1136/archdischild-2020-319063. PubMed PMID: 32859738.
169. Fenton TR, Merlino Barr S, Elmrayed S, Alshaikh B. Expected and Desirable Preterm and Small Infant Growth Patterns. Adv Nutr. June, 2024;15(6):100220. Epub 20240424. doi: 10.1016/j.advnut.2024.100220. PubMed PMID: 38670164; PubMed Central PMCID: PMC11251411.
170. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. December 1, 1993;138(11):923–36. doi: 10.1093/oxfordjournals.aje.a116813. PubMed PMID: 8256780.
171. Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. Kidney Int. February, 2008;73(3):256–60. Epub 20071031. doi: 10.1038/sj.ki.5002650. PubMed PMID: 17978811.
172. Simon S. What is residual Confounding? Pmean 2010. Available from: http://www.pmean.com/10/ResidualConfounding.html.
173. González-Fernández D, Williams TS, Vaivada T, Bhutta ZA. Early Growth and Impacts on Long-Term Neurodevelopment and Human Capital. Ann Nutr Metab. November 27, 2024:1–14. Epub 20241127. doi: 10.1159/000540874. PubMed PMID: 39602892.
174. Dahiya P, Shweta, Parashar A, Lohakare T. A Study on the Effect of Umbilical Cord Milking Along With Delayed Cord Clamping on Hematological Parameters in Comparison to Delayed Cord Clamping Alone in Moderate-to-Late Preterm Newborns. Cureus. September 12, 2024;16(9):e69256. Epub 20240912. doi: 10.7759/cureus.69256. PubMed PMID: 39403649; PubMed Central PMCID: PMC11472205.
175. Robledo KP, Tarnow-Mordi WO, Rieger I, Suresh P, Martin A, Yeung C, et al. Effects of delayed versus immediate umbilical cord clamping in reducing death or major disability at 2 years corrected age among very preterm infants (APTS): a multicentre, randomised clinical trial.

Lancet Child Adolesc Health. March, 2022;6(3):150–7. Epub 20211208. doi: 10.1016/s2352-4642(21)00373-4. PubMed PMID: 34895510.
176. Ricci MF, Shah PS, Moddemann D, Alvaro R, Ng E, Lee SK, et al. Neurodevelopmental Outcomes of Infants at <29 Weeks of Gestation Born in Canada Between 2009 and 2016. J Pediatr. August, 2022;247:60–6.e1. Epub 20220511. doi: 10.1016/j.jpeds.2022.04.048. PubMed PMID: 35561804.
177. Tarnow-Mordi WO, Robledo K, Marschner I, Seidler L, Simes J. To guide future practice, perinatal trials should be much larger, simpler and less fragile with close to 100% ascertainment of mortality and other key outcomes. Semin Perinatol. August, 2023;47(5):151789. Epub 20230611. doi: 10.1016/j.semperi.2023.151789. PubMed PMID: 37422415.
178. Kim HA, Park SH, Lee EJ. Iron status in small for gestational age and appropriate for gestational age infants at birth. Korean J Pediatr. March, 2019;62(3):102–7. Epub 20181024. doi: 10.3345/kjp.2018.06653. PubMed PMID: 30360035; PubMed Central PMCID: PMC6434228.
179. Brown BE, Shah PS, Afifi JK, Sherlock RL, Adie MA, Monterrosa LA, et al. Delayed cord clamping in small for gestational age preterm infants. Am J Obstet Gynecol. February, 2022;226(2):247.e1–.e10. Epub 20210809. doi: 10.1016/j.ajog.2021.08.003. PubMed PMID: 34384773.
180. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. Delayed versus Immediate Cord Clamping in Preterm Infants. N Engl J Med. December 21, 2017;377(25):2445–55. Epub 20171029. doi: 10.1056/NEJMoa1711281. PubMed PMID: 29081267.
181. Chiruvolu A, Tolia VN, Qin H, Stone GL, Rich D, Conant RJ, et al. Effect of delayed cord clamping on very preterm infants. Am J Obstet Gynecol. November 1, 2015;213(5):676.e1–7. Epub 20150718. doi: 10.1016/j.ajog.2015.07.016. PubMed PMID: 26196456.
182. Nevill E, Meyer MP. Effect of delayed cord clamping (DCC) on breathing and transition at birth in very preterm infants. Early Hum Dev. July, 2015;91(7):407–11. Epub 20150515. doi: 10.1016/j.earlhumdev.2015.04.013. PubMed PMID: 25984654.
183. Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev. October, 2004(4):Cd003248. Epub 20041018. doi: 10.1002/14651858.CD003248.pub2. PubMed PMID: 15495045.
184. Wang T, Wang S, Zhou M, Duan Y, Chen W, Pan L, et al. Impact of delayed cord clamping on respiratory distress in late preterm and early term infants in elective cesarean section: a single centre, phase III, randomised controlled trial. EClinicalMedicine. February 26, 2025;81:103126. Epub 20250226. doi: 10.1016/j.eclinm.2025.103126. PubMed PMID: 40093988; PubMed Central PMCID: PMC11909439.
185. Dassios T, Kaltsogianni O, Belani P, Arasu A, Greenough A. Cumulative hypoxia, socioeconomic deprivation and neurodevelopmental outcomes in preterm infants. Respir Physiol Neurobiol. November, 2022;305:103942. Epub 20220628. doi: 10.1016/j.resp.2022.103942. PubMed PMID: 35777720.
186. Murki S, Kallem VR, Gururaj J, Bashir T, Oleti TP, Kiran S. Growth and Neurodevelopmental Outcomes at 12 to 18 Months of Corrected Age in Preterm Infants Born Small for Gestational Age. Indian Pediatr. February 5, 2020;57(4):301–4. Epub 20200205. PubMed PMID: 32038032.
187. Girsen A, Do S, El-Sayed YY, Blumenfeld YJ. 109: Association between small-for-gestational-age and neurodevelopmental impairment at two years of life among infants born at preterm gestational ages. American Journal of Obstetrics & Gynecology. January 1, 2016;214(1):S76.

188. Tsamantioti E, Lisonkova S, Muraca G, Örtqvist AK, Razaz N. Chorioamnionitis and risk of long-term neurodevelopmental disorders in offspring: a population-based cohort study. Am J Obstet Gynecol. August, 2022;227(2):287.e1–.e17. Epub 20220316. doi: 10.1016/j.ajog.2022.03.028. PubMed PMID: 35305960.
189. Bourgoin L, Cipierre C, Hauet Q, Basset H, Gournay V, Rozé JC, et al. Neurodevelopmental Outcome at 2 Years of Age according to Patent Ductus Arteriosus Management in Very Preterm Infants. Neonatology. January 5, 2016;109(2):139–46. Epub 20160105. doi: 10.1159/000442278. PubMed PMID: 26726863.
190. Squarza C, Gardon L, Giannì ML, Frigerio A, Gangi S, Porro M, et al. Neurodevelopmental Outcome and Adaptive Behavior in Preterm Multiples and Singletons at 1 and 2 Years of Corrected Age. Front Psychol. July 8, 2020;11:1653. Epub 20200708. doi: 10.3389/fpsyg.2020.01653. PubMed PMID: 32733348; PubMed Central PMCID: PMC7360726.
191. Christensen R, Chau V, Synnes A, Guo T, Ufkes S, Grunau RE, et al. Preterm Sex Differences in Neurodevelopment and Brain Development from Early Life to 8 Years of Age. J Pediatr. January, 2025;276:114271. Epub 20240830. doi: 10.1016/j.jpeds.2024.114271. PubMed PMID: 39218208.
192. Fewtrell MS, Kennedy K, Singhal A, Martin RM, Ness A, Hadders-Algra M, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child. June, 2008;93(6):458–61. doi: 10.1136/adc.2007.127316. PubMed PMID: 18495909.
193. Doucette SM, Tang S, Kehler H, Creighton D, Lodha A. Utility of the 21-month neurodevelopmental outcome for predicting neurodevelopmental impairment at 36 months for preterm infants <29 weeks gestation. J Perinatol. September 15, 2023;43(11):1406–12. Epub 20230915. doi: 10.1038/s41372-023-01777-3. PubMed PMID: 37714894.
194. Lin CY, Hsu CH, Chang JH. Neurodevelopmental outcomes at 2 and 5 years of age in very-low-birth-weight preterm infants born between 2002 and 2009: A prospective cohort study in Taiwan. Pediatr Neonatol. February, 2020;61(1):36–44. Epub 20190614. doi: 10.1016/j.pedneo.2019.05.006. PubMed PMID: 31278044.
195. Taylor GL, Joseph RM, Kuban KCK, Douglass LM, Laux J, Andrews B, et al. Changes in Neurodevelopmental Outcomes From Age 2 to 10 Years for Children Born Extremely Preterm. Pediatrics. April 6, 2021;147(5). Epub 20210406. doi: 10.1542/peds.2020-001040. PubMed PMID: 33824183; PubMed Central PMCID: PMC8086004.

APPENDIX A: SAMPLE SIZE CALCULATION

The power was calculated using the formula for comparing proportions in two independent groups, given by Kelsey et al. in Table 2, page 330 (137).

$$Z_{\beta} = [\, n(d^{*})^{2} r/(r+1)\, \tilde{p}\,(1-\tilde{p})]^{1/2} - Z_{\alpha/2},$$

Where:

- n = 153 (at 18-24 months follow-up) and 145 (at 36 months follow-up)
- Difference, d^{*}= P1-P0 = -0.14
- Unexposed to exposed ratio, r = 2
- Weighted average of P1 and P0, $\tilde{P}$= P1 + rP0/1+r = 0.29
- Z1−α/2 is the critical value for a two-tailed test at α=0.05 (1.96)

Calculation for 18-24 months Follow-up

- The proportion of unexposed who develop the disease, P0 = 0.34
- RR = 0.60
- The proportion of exposed who develop the disease, P1 = P0*RR

  = 0.34*0.60

  = 0.20
- Difference, d^{*}= P1-P0 = 0.20- 0.34 = -0.14
- Unexposed to exposed ratio, r = 414/153 = 2
- Weighted average of P1 and P0, $\tilde{P}$= P1 + rP0/1+r

  = 0.20 + 2*0.34/ 1+ 2 = 0.20+ 0.68/3

  = 0.88/ 3 = 0.29

- Sample size, no of cases, n = 153
- $Z_{\alpha/2}$= 1.96
- $Z_{\beta} = [\ n(d^{*})^2 r/(r+1)\ \tilde{p}\ (1-\tilde{p})]^{1/2} - Z_{\alpha/2}$

  $= [\ 153*\ (-0.14)^2*2/\ 3*.29(1-\ 0.29)]^{1/2}\ \ -1.96$

  $= (6/0.62)^{1/2} -1.96 = (9.68)^{1/2} - 1.96 = 3.11 -1.96$

  $= 1.15$

The power of detecting association between deferred cord clamping (DCC) and long-term neurodevelopmental outcomes at 18-24 months, based on Table 12-14, p-331 at Kelse et al. is calculated 87.5%.

Calculation for 36 months follow-up

- The proportion of unexposed who develop the disease, P0 = 0.34
- RR = 0.60
- The proportion of exposed who develop the disease, P1 = P0*RR

  $= 0.34*0.6 = 0.20$
- Difference, d^{*}= P1-P0 = 0.20- 0.34 = -0.14
- Unexposed to exposed ratio, r = 376 /145 = 2
- Weighted average of P1 and P0, $\tilde{P}$= P1 + rP0/1+r

  $= 0.20 + 2*0.34/3 = 0.20+ 0.68/3$

  $= 0.88/\ 3 = 0.29$
- Sample size, no of cases, n = 145
- $Z_{\alpha/2}$= 1.96
- $Z_{\beta} = [\ n(d^{*})^2 r/(r+1)\ \tilde{p}\ (1-\tilde{p})]^{1/2} - Z_{\alpha/2}$

  $= [\ 145*\ (-0.14)^2*2/\ 3*0.29(1-\ 0.29)]^{1/2}\ \ -1.96$

$= (5.68/0.62)^{1/2} - 1.96 \qquad = (9.16)^{1/2} - 1.96 \qquad = 3.03 - 1.96$

$= 1.07$

The power of detecting association between deferred cord clamping (DCC) and long-term neurodevelopmental outcomes at 36 months based on Table 12-14, p-331 at Kelse et al. is calculated 85.8%.

From the power calculation, it was revealed that our study's power to identify a relative risk of 0.60 was 87.5% for 18–24 months analysis, and 85.8% for 36 months analysis. This indicates that we had the sufficient sample size to provide adequate power to detect a reasonable effect size as large as the desired relative risk of 0.60 and to achieve statistical reliability and validity for the comparisons.

APPENDIX B: DATA DICTIONARY

Table B.1. Transformation and coding of final variables (NICU Database)

Variable Name	Code & Label	Variable Type	Name, Code & Label in the Original Database
Cord Clamping	0 = Immediate cord clamping (ICC). 1 = Deferred cord clamping (DCC).	Categorical, binary	**DCordClamping (NICU Database)** Yes No Unknown
Maternal Age	N/A	Continuous	**MAGE**
Completed High School	0 = no (**EDUCM:** code1–3). 1 = yes (**EDUCM:** code 4–7).	Categorical, binary	**EDUCM:** 1 = ≤ grade 7; 2 = grade 8-9; 3 = grade 10-11, 4 = high school graduate; 5 = some university/specialty training (includes any post-secondary education, excluding a university/college degree, partially completed program); 6 = college/university graduate (completed program/certificate/degree; 7 = graduate degree.
Pregnancy Induced Hypertension (PIH)	0 = no (**MATHYP:** code 0, 2,3). 1 = yes (**MATHYP:** code 1, 4).	Categorical, binary	**MATHYP**: 0= <140/90; 1 = PIH; 2 = pre-pregnancy ≥ 140/90 with antihypertensive drugs; 3 = pre-pregnancy ≥ 140/90 without antihypertensive drugs; 4 = pre-pregnancy hypertension with pregnancy induced hypertension superimposed.
Gestational Diabetes	0 = no (**MATDIAB** code 0,2,3). 1 = yes (**MATDIAB:** code 1).	Categorical, binary	**MATDIAB**: 0 = no, 1 = gestational diabetes, 2 = non-gestational diabetes with insulin; 3 = non-gestational diabetes without insulin.
Chorioamnionitis	0 = no **(CHORIO:** code 0) 1 = yes **(CHORIO:** code 1).	Categorical, binary	**CHORIO:** 0 = no, 1 = yes.
Caesarean delivery	0 = Vaginal Delivery. (**CSEC:** code 0).	Categorical, binary	**CSEC:** Caesarean section delivery, 0 = no 1 = yes.

	1 = Caesarean section (**CSEC:** code 1).		
Antenatal Corticosteroids (ANCS)	0 = no (**LDSTER:** code 0). 1 = yes (**LDSTER:** code 1).	Categorical, binary	**LDSTER:** Use of antenatal steroids/glucocorticoids during labour and delivery, 0 = no; 1 = yes.
Maternal Antibiotics	0 = no (**LDANTI:** code 0). 1 = yes (**LDANTI:** code 1).	Categorical, binary	**LDANTI:** Administration of antibiotics to the mother during labour and delivery, 0 = no; 1 = yes.
Multiparous	0 =Nulliparous (**TERM**=0, **PRETERM** =0). 1=Multiparous.	Categorical, binary	**TERM =** The number of term births prior to this delivery. **PRETERM =** The number of preterm births prior to this delivery.
Multiple Birth	0 = Single pregnancy (**MB:** code 0). 1 = Twin/triplet (**MB:** code 1, 2).	Categorical, binary	**MB:** 0 = singleton; 1 = twins; 2 = triplets or greater
Prolonged rupture of the membrane (PROM)	0 = membrane rupture <24 hours (**ROM:**code 1). 1 = membrane rupture >24 hours (**ROM:** code 2, 3, 4, 8).	Categorical, binary	**ROM:** Timing of membrane rupture in relation to the time of delivery, 1=<24 hours; 2=24-48 hours; 3=2-14 days; 4= >14 days; 8= ≥ 24 hours, extent unknown.
Smoking	0 = no (**SMOKE:** code 0). 1 = yes (**SMOKE:** code 1).	Categorical, binary	**SMOKE:** maternal smoking at any time during this pregnancy, 0= no; 1 = yes
Alcohol use	0 = No or occasional alcohol use (**ALCOHOL:** code 0). 1 = yes (**ALCOHOL:** code 1, 4).	Categorical, binary	**ALCOHOL:** maternal alcohol abuse at any time during this pregnancy, 0= no or occasionally during pregnancy; 1= yes; 4= suspect.
Material Deprivation Quintiles	Quintile1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	Ordinal	Residential postal codes for mothers in the DCC and ICC group were linked with the 2016 & 2011 Pampalon deprivation index
Social Deprivation Quintiles	Quintile1 Quintile 2 Quintile 3	Ordinal	Residential postal codes for mothers in the DCC and ICC group were linked with

	Quintile 4 Quintile 5		the 2016 & 2011 Pampalon deprivation index
Materially deprived	0 = not deprived (Quintiles1, 2, 3) 1 = deprived (Quintiles 4, 5)	Categorical, binary	
Socially deprived	0 = not deprived (Quintiles1,2,3) 1 = deprived (Quintiles 4,5)	Categorical, binary	
Gestational age	NA	Continuous	**GEST:** Fully completed gestational weeks at birth
Birth weight	NA	Continuous	**BW:** Birth weight in grams.
Male sex	0 = female (**SEX:** code 2) 1 = male (**SEX:** code 1)	Categorical, binary	**SEX:** 1= male; 2= female.
Small for gestational age (<10th percentile) (SGA)	0 = No SGA 1 = SGA	Categorical, binary	**SGA** status was calculated by using gestational age and birth weight on Fenton growth chart calculator
Apgar score at 5 minutes <7	0 = ≥7 at 5 minutes after birth. 1 = <7 at 5 minutes after birth.	Categorical, binary	**AP5:** Apgar score at 5 minutes after birth.
RDS	0 = no (**RDS:** code 0) 1 = yes (**RDS:** code 1)	Categorical, binary	**RDS:** Hyaline membrane disease/respiratory distress syndrome. Must be radiographically confirmed and/or treated with oxygen or surfactant for>72 hours, 0=no; 1= yes.
BPD	0 = no (**O36:** code 0) 1 = yes (**O36:** code 1)	Categorical, binary	**O36:** Indicates if the child was on respiratory support at 36 weeks gestational age, 0= no; 1= yes.
PDA	0 = no (**PDA:** code 0) 1 = yes (**PDA:** code 1, 2, 3)	Categorical, binary	**PDA:** 0= none, 1= treated surgically, 2= treated medically, 3 = yes, no treatment
Surg. treated PDA	0 = no (**PDA:** code 0, 2&3) 1 = yes (**PDA:** code 1)	Categorical, binary	**PDA:** 0= none, 1= treated surgically, 2= treated medically, 3 = yes, no treatment
Sepsis	0 = no (**SEPSIS:** code 0, 2)	Categorical, binary	**SEPSIS:** 0= none (negative cultures, no clinical signs, no risk factors, no

	1 = cultured confirmed sepsis (**SEPSIS:** code 1)		antibiotics); 1= confirmed (positive blood or CSF culture), 2= presumed (negative cultures and treated with antibiotics for ≥ 48 hours).
IVH	0 = no (code 0) 1 = yes (code 1, 2, 3, 4, 8)	Categorical, binary	**IVHGRADE:** Presence and severity of IVH (clinical/ultrasound/CT/MRI), worst side, 0 = no IVH; 1 = grade I; 2 = grade 2; 3 = grade 3; 4 = grade 4; 8 = grade unknown.
Severe IVH	0 = no (code 0, 1, 2, 8) 1 = yes (code 3, 4)	Categorical, binary	**IVHGRADE:** Presence and severity of IVH, (clinical/ultrasound/CT/MRI), worst side, 0 = no IVH; 1 = grade I; 2 = grade 2; 3 = grade 3; 4 = grade 4; 8 = grade unknown.
PVL	0= no (**PVL:** code 0) 1 = yes (**PVL:** code 1**)**	Categorical, binary	**PVL:** Evidence of brain lesions in the white matter which may be confirmed by development of multiple bilateral cysts on MRI/ultrasound, 0= no; 1= yes.
SNI	0 = no (code 0, 1, 2 from **IVHGRADE** and code 0 from **PVL**)) 1 = yes (code 3, 4 from **IVHGRADE** and/or code 1 from **PVL**)	Categorical, binary	**IVHGRADE:** Presence and severity of IVH (clinical/ultrasound/CT/MRI), worst side, 0 = no IVH; 1 = grade I; 2 = grade 2; 3 = grade 3; 4 = grade 4; 8 = grade unknown. **PVL:** Evidence of brain lesions in the white matter which may be confirmed by development of multiple bilateral cysts on MRI/ultrasound, 0= no; 1= yes.
NEC	0 = no (**NEC:** code 0) 1 = yes (**NEC:** code 1)	Categorical, binary	**NEC:** must have x ray evidence of NEC, 0= no; 1= yes (≥ stage 2 NEC)
ROP	0 = no (code 0) 1 = yes (code 1, 2, 3, 4, 5, 7, 8)	Categorical, binary	**ROPRNICU & ROPLNICU:** 0=no ROP; 1= stage 1; 2= stage 2; 3= stage 3; 4= stage 4; 5= stage 5; 7 = plus disease (between stage 3 &4); 8= stage unknown.
Severe ROP	0 = no (code 0, 1, 2, 8) 1= yes (code 3, 4, 5, 7)	Categorical, binary	**ROPRNICU & ROPLNICU:** 0=no ROP; 1= stage 1; 2= stage 2; 3= stage 3; 4= stage 4; 5= stage 5; 7 = plus disease (between stage 3 &4); 8= stage unknown.
Discharge home on oxygen	0 = no (**O2DC:** code 0) 1 = yes (**O2DC:** code 1**)**	Categorical, binary	**O2DC:** If the infants were discharged home on oxygen, 0=no; 1= yes, home.

Number of transfusions	N/A	Continuous	**RBC:** Number of times packed RBC's and/or whole blood were given.
Total ventilation	N/A	Continuous	**MVENTDAYS:** Duration of days on mechanical ventilation (IPPV or HFOV/jet/osc.
Total non-invasive resp. Support	N/A	Continuous	**RESPDAYS:** Duration of non-invasive respiratory support (CPAP/SiPAP/ High flow≥1.5LPM.
Total suppl. oxygen	N/A	Continuous	**O2DAYS:** Total number of days an infant was on oxygen support.
NICU stay	N/A	Continuous	**DAYSHOSP:** Total days in hospital until discharged home.

Table B.2. Transformation and coding of final variables (NFC Database)

Variable Name	**Code & label**	**Variable Type**	**Name, Code & Label in the original Database**
Death	0 = not died (**DISP:** code 0) 1 = died (**DISP:** code 5, 7)	Categorical, binary	**DISP:** 0= not died; 5 = died before discharge home; 7 = died after discharge home
Cerebral Palsy	0= no (**CP:** code 0**)** 1 = yes (**CP:** code 1)	Categorical, binary	**CP:** 0= no; 1 = yes; 4= suspect but doubtful; 5 = suspect but probable; 6 = suspect, conveyed to parents/guardians (historical data only)
Cognitive/motor/language delay	0= no delay 1 = detected as cognitive/motor/language delay (Bayley III/IV <85, WPPSI III/IV (FSIQ), Leiter-R/ <85)	Categorical, binary	**COG:** Bayley III/IV (cognitive composite score), WPPSI III/IV (FSIQ), Leiter-R/3 (Full IQ) **PSYTEST:** 0 = WPPSI-IV; 2 = WPPSI-III; 8 = Bayley III; 13 = Leiter-R. **BAYLC:** Bayley IV language composite score.

			BAYMC: Bayley IV motor composite score.
Hearing Impairment	0= no impairment (**HEAR_IMP_OLD** code 0; **HEAR_L & HEAR_R** code 0; **NATLOSS_L & NATLOSS_R** code 0, 2 **AID** code 0**)** 1 = had impairment (**HEAR_IMP_OLD:** code 1, 2, 3, 4; **HEAR_L & HEAR_R** code 1, 2; **NATLOSS_L & NATLOSS_R** code 1, 4, 5; **AID** code 1, 2, 4**)** If no **HEAR_IMP_OLD** and no **HEAR_L** and no **HEAR_R**, use **HEARING_P** (code 1,2,4,5,6).	Categorical, binary	**HEAR_IMP_OLD:** 0= none; 1= severe to profound (>70 dB); 2 = moderate (50-70dB); 3 = mild (25-45dB); 4 = unilateral sensory neural hearing loss. **AID:** 0=none; 1= one year; 2 = both years; 4 = yes, unknown (one or both ear) **HEAR_L & HEAR_R:** 0 = no hearing loss; 1 = severe to profound loss (71-90 dB or >90 dB); 2 = mild to moderate loss (26-40dB, 41-55 dB or 56-70 dB); 3 = unreliable assessment. **NATLOSS_L & NATLOSS_R:** 0 = no hearing loss, 1 = sensorineural, 2 = conductive; 4 = mixed; 5 = auditory neuropathy. **HEARING_P:** 0 = no hearing loss or conductive loss only; 1 = bilateral neurosensory loss requiring amplification/ cochlear implants; 2 = unilateral neurosensory loss requiring amplification; 4 = neurosensory hearing

			loss not requiring amplification/ cochlear implants; 5 = auditory neuropathy requiring amplification/ cochlear implants; 6 = auditory neuropathy not requiring amplification/ cochlear implants
Visual Impairment	0 = no impairment (include code 0 from **VISIMP, BILATBLIND, VISION_P,)** 1 = had impairment (**VISIMP** code 1, 2 &3 or **BILATBLIND** code 1,2 &3. If no **VISIMP** and no **BILATBLIND,** use **VISION_P** code 1, 2, 4).	Categorical, binary	**VISIMP:** 0 = no, (no significant visual impairment); 1 = yes (corrected visual acuity between <20/60 and >20/200, Teller acuity less than age-level but not bilaterally blind; 2 = significant refractive errors such as severe myopia (>-8.00), significant hyperopia (>+4.00) or amblyopia (if visual acuity not obtained; 3 = yes, unilateral blindness. **BILATBLIND:** 0= no (not bilaterally blind; 1= yes, corrected visual acuity<20/200 in better eye or Teller acuity less than age level; 2 = yes, visual acuity not obtained but registered or referred to CNIB and clinical diagnosis of bilateral blindness; 3 = yes, visual acuity not obtained but cortical blindness or atrophy. **VISION_P:** 0 = normal; 1 = bilateral

			blindness; 2 = uncorrected visual acuity between <20/60 and >20/200; 3 = unreliable assessment; 4 = mild impairment.
NDI	0= no NDI 1 = detected as NDI (**CP** = yes; **GMFCS** ≥1; **COG/BAYLC/ BAYMC**= <85; **HEAR_IMP_OLD** code 1, 2, 3, 4 **HEARING_P** (code 1, 2, 4, 5, 6) **AID:** code 0, 1, 2, 4; **VISIMP** code 1, 2, 3 or **BILATBLIND** code 1, 2, 3. If no **VISIMP** and no **BILATBLIND,** use **VISION_P** code 1, 2, 4**)**.	Categorical, binary	**CP** **GMFCS** **COG** **PSYTEST** **BAYLC** **BAYMC** **HEAR_IMP_OLD** **HEAR_L** **HEAR_R** **NATLOSS_L** **NATLOSS_R** **HEARING_P** **AID** **VISION_P** **VISIMP** **BILATBLIND**
Severe NDI	0= no severe NDI 1 = detected as severe NDI (**CP** = yes; **GMFCS** ≥3; **COG/BAYLC/ BAYMC**= <70 **HEAR_IMP_OLD, HEARING_P & AID** = bilateral sensorineural hearing loss or auditory neuropathy with aid. **VISION_P, VISIMP & BILATBLIND** = bilateral blindness.	Categorical, binary	**CP** **GMFCS** **COG** **PSYTEST** **BAYLC** **BAYMC** **HEAR_IMP_OLD** **HEAR_L** **HEAR_R** **NATLOSS_L** **NATLOSS_R** **HEARING_P** **AID** **VISION_P** **VISIMP** **BILATBLIND**
Growth	N/A	Continuous	**WT=** Weight (kg). **HT=** Length/Height (cm). **HC=** Head circumference (cm).